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ANNALS OF INTERNAL MEDICINE

VOLUME 25

JULY, 1946

NUMBER 1

ESSENTIAL ORAL HYPERTHERMIA; REPORT OF A STUDY OF 25 CASES OF LOW GRADE 'FEVER' *

By EMANUEL M. RAPPAPORT, Captain, M.C., A.U.S., *Clinton, Iowa*

THERE are few problems confronting the internist more challenging, vexing and yet intriguing than fever which persists for weeks or months without yielding a single clue as to its origin. Not infrequently, time or the laboratory establishes the diagnosis. With the elapse of a sufficient period of observation, some leading symptom or clinical finding becomes manifest or one of the usually numerous laboratory tests enlisted in the search yields the clue to solution.

The upper limit of normal oral temperature is almost universally regarded as 99° F. with rectal temperature one-half to three-quarters degree higher. Wright¹ accepts the range as 96.7 to 99° F. and 97.2 to 99.5° F. respectively, the rectal being generally considered the more reliable mode of determination. Kintner and Rowntree² believe that a continuous mouth temperature of 99° F. or over in an adult represents fever whether or not the person is nervous.

That elevation of oral temperature per se cannot be regarded as the sole criterion of either fever or organic disease may be adduced from the following survey of 25 cases admitted to the Medical Service of a general hospital with the diagnosis 'fever of undetermined origin.' Each had been observed at one or more hospitals for an average period of 16.3 weeks and had undergone extensive laboratory investigation for cryptogenic sepsis to no avail. Studies here disclosed that all exhibited an elevated oral temperature associated with normal rectal temperature. It is the purpose of this presentation to advance clinical evidence which favors an inherent vasomotor instability as the etiological basis of this paradox.

Consideration of these cases will be undertaken with regard to the following:

* Received for publication February 5, 1946.

From the Medical Service, Schick General Hospital, Clinton, Iowa.

1. Cause of original hospitalization
2. Symptomatology
3. Objective findings—
 - a. Clinical
 - b. Laboratory
4. Fever
5. Diagnosis
6. Management
7. Disposition and follow-up

1. *Cause of original hospitalization* (table 1). Twenty-two patients were originally hospitalized because of a well-defined febrile disease, and when all clinical signs of infection had subsided, it was noted that a persistent low-grade fever remained, resulting in a prolonged search for its etiology. Three patients were admitted primarily for treatment of disorders not usually associated with fever (duodenal ulcer, migraine, and lumbosacral strain), the elevated temperature being discovered upon routine check.

TABLE I
Cause of Original Hospitalization

Admission Diagnosis	Number
Acute upper respiratory infection..	18
Bacillary dysentery.....	2
Malaria..	1
Herpes zoster..	1
Duodenal ulcer...	1
Migraine... ..	1
Lumbosacral strain.	1
	<hr/> 25

2. *Symptomatology*. The usual symptoms of prolonged fever are malaise, exhaustion, anorexia, headache, nervousness, palpitation and weight loss. These complaints were registered by nearly all, particularly those who had been under observation for several months or more. Twenty-two experienced the sensation of fever to a varying degree; four of this group stated they had frequent chills. Such non-specific symptoms as fleeting precordial, muscle and joint pains, irritability, depression and insomnia were frequent. Hyperhidrosis of the palms and soles was a particular source of distress. Repeated interview, however, disclosed a constantly altering pattern of symptoms in the individual patient.

3. *Objective findings*. a. *Clinical*: Subjective complaints were rarely authenticated by objective evidence of disease. Despite the invariable complaints of anorexia and weight loss, comparison of weight upon admission to this hospital with that recorded at onset of illness revealed insignificant fluctuation. Fifteen were unchanged, five had gained and two had lost less than 5 per cent of their original body weight. They looked remarkably well despite protracted fever. Three patients were 12 to 15 pounds below their initially recorded weight. One of the latter had regained all lost weight during a 30-day furlough from another hospital, but gradually lost it again during 20 weeks of further hospitalization.

Dysorexia is a common sequel of prolonged hospitalization in the army and yet is frequently unattended by appreciable weight reduction. This is

due to curtailed activity with resultant diminished requirement for the high caloric intake customary during active field duty. The hypochondriac is inclined to view this physiologic loss of appetite with alarm.

The most constant finding was marked hyperhidrosis affecting the palms, soles and axillae. Although blood pressure showed little variation upon repeated recording, considerable fluctuation of pulse rate was in evidence. Tachycardia, however, did not always coincide with the period of maximum daily temperature, contrary to the pulse-temperature relationship characteristic of infectious fevers.

It is noteworthy that all patients whose hospitalization had been initiated by infection listed fever among their chief complaints. Of the three whose fever had been discovered in the routine temperature check, only one felt 'feverish' and he dated the onset of this symptom to his sixth week of hospitalization (case 25, table 2). Eight patients reported that they experienced a sudden sensation of 'burning up' at approximately the same time each day, usually in the late afternoon. This frequently but not invariably coincided with the peak of oral temperature, although rectal level was consistently normal.

Few of the numerous and varied subjective complaints could be corroborated by objective findings of deranged function or physical deterioration. This is not to be construed as evidence of malingering, but as the product of a pathological preoccupation with somatic sensations to which prolonged hospitalization contributes in no small measure. Thus two soldiers (cases 6 and 9, table 2) who were originally observed because of upper respiratory infection were eventually studied exhaustively with regard to diarrhea. Both had been aware of post-prandial evacuation of formed stools for many years and had displayed no apprehension regarding this frequency until after an inquiry had been begun regarding the cause of persistent fever, whereupon they developed marked 'bowel-consciousness.'

As a group they displayed lassitude, failed to engage in ward activities despite being ambulant, remained seclusive, asocial and exhibited considerable anxiety regarding the ultimate outcome of their disease. Three had purchased thermometers and were accustomed to take their oral temperature at frequent intervals during the day. Nearly all parried the suggestion that oral fever alone was not significant of disease with such reasonable rebuttals as, "Everybody knows a person with fever is sick" or "If I have fever I must be sick."

b. *Laboratory*: Although there are notable exceptions, it is anticipated that at some period during the course of a prolonged febrile disease progressive anemia, an alteration of the white blood count and Schilling index, or an increase of sedimentation rate would be found. Nevertheless in not a single instance were deviations from normal encountered upon repeated examination.

Prior to admission to this hospital, in addition to routine tests, studies included stools, sputum, gastric contents, liver function, prostatic smears,

TABLE II

Case No.	Age	Cause of Original Hospitalization	Period of Observation*	Temperature†		Final Diagnosis	Disposition	Interval (months)	Subsequent Course
				Oral	Rectal				
1	21	Tonsillitis	36	99.8	99.4	N.C.A.‡	Discharge	4	Working on farm; fatigued and nervous.
2	24	Tonsillitis	8	99.4	99.6	Psychoneurosis (mixed)	Discharge	—	—
3	23	Tonsillitis	17	99.6	99.4	Psychoneurosis (mixed)	Duty	6	Oral temp. normal when released from hospital; doing army clerical work; fatigues; no symptoms of fever; has not taken temp.
4	22	Acute upper resp.	15	99.6	99.6	N.C.A.	Duty	3	No improvement; fatigue, headaches, and malaise; does not mention fever.
5	24	Acute upper resp.	4	99.6	99.4	No disease	Duty	—	—
6	20	Acute upper resp.	10	99.4	99.4	Psychoneurosis (anxiety)	Duty	4	Discharged from army after 2 months because of "nervousness."
7	26	Acute upper resp.	13	99.5	99.6	Psychoneurosis (anxiety)	Duty	3	Discharged from army because of "fatigue and nervousness."
8	23	Acute upper resp.	12	99.4	99.4	Psychoneurosis (anxiety)	Duty	—	Working as mechanic; feels well. Does not believe he has fever.
9	25	Acute upper resp.	20	99.8	99.5	N.C.A.	Discharge	5	Mouth temp. normal; fatigues and perspires easily.
10	26	Pharyngitis	18	99.6	99.6	Psychoneurosis (mixed)	Discharge	3	Tires readily; still nervous. No mention of temperature.
11	21	Acute upper resp.	14	99.6	99.4	Psychoneurosis (mixed)	Discharge	4	"Thinks his mouth temperature is normal." Improved, but tires easily. Working on farm.

* Weeks of continuous hospitalization prior to admission to general hospital.

† Average peak during 10-day period.

‡ Neurocirculatory asthenia.

TABLE II—Continued.

Case No.	Age	Cause of Original Hospitalization	Period of Observation*	Temperature†		Final Diagnosis	Disposition	Subsequent Course	
				Oral	Rectal			Interval (months)	Report of Progress
12	20	Acute upper resp.	32	99.4	99.6	Psychoneurosis (anxiety)	Discharge	3	Managing grocery. Easily upset but feels stronger. No note about temperature.
13	21	Acute upper resp.	10	99.4	99.4	N.C.A.	Duty	—	—
14	22	Acute upper resp.	13	99.4	99.4	N.C.A.	Duty	—	—
15	26	Acute upper resp.	17	99.7	99.5	Psychoneurosis (anxiety)	Discharge	3	Improved but easily excited. Farming; no mention of fever.
16	24	Acute upper resp.	4	99.6	99.4	N.C.A.	Duty	—	—
17	28	Pharyngitis	5	99.4	99.6	No disease	Duty	5	Asymptomatic; oral temperature under 99°.
18	28	Acute upper resp.	8	99.4	99.5	N.C.A.	Duty	4	No improvement. Palpitation and fatigue.
19	23	Bacillary dys.	14	99.6	99.4	N.C.A.	Discharge	3	Easy fatigue and nervous under tension; farming; no note on fever.
20	28	Herpes zoster	23	99.8	99.2	Hysteria	Discharge	—	—
21	21	Bacillary dys.	50	99.3	99.4	Psychoneurosis (mixed)	Discharge	4	Still "nervous"; has no fever. Inspector in machine shop.
22	24	Malaria	40	99.7	99.4	N.C.A.	Duty	—	—
23	21	Duod. ulcer	10	99.4	99.4	Duod. ulcer N.C.A.	Discharge	4	Still has heartburn, palpitations, and fatigue; no mention of fever.
24	23	Lumbosacral strain	6	99.6	99.6	Psychoneurosis (mixed)	Discharge	—	—
25	27	Migraine	9	99.5	99.6	Hysteria	Discharge	—	—

basal metabolic rate, electrocardiogram, blood cultures, chest roentgenograms, and skin tests for tuberculosis, brucellosis, and occasionally coccidioidomycosis. Proctoscopy, bone marrow biopsy, spinal puncture and roentgen examination of the gall-bladder, gastrointestinal and urinary tracts were performed when indicated. All these diverse diagnostic procedures which were necessitated by the heterogeneous complaints that appeared to implicate various systems, were normal.

4. *Fever.* The transfer diagnosis, 'fever of undetermined origin,' was based upon the presence of a daily elevation of oral temperature above 99° F. without rectal controls. It was the probable, and not unreasonable, assumption of previous examiners that oral hyperthermia would be attended by a comparable rise in rectal temperature. The presence of an abnormally high oral temperature was confirmed by four-hourly determinations, but rectal temperature remained consistently normal. Temperature studies were conducted four-hourly over a 10-day period or longer, with close observation of the patient during the time of actual recording. Smoking, gum-chewing and physiologic post-prandial elevation of mouth temperature were ruled out as possible factors. Oral hyperthermia was considered established by the demonstration of repeated oral levels above 99.2° F. in the presence of rectal temperature of 99.6° or below. Cases exhibiting rectal temperature above 99.6° were excluded from this series, despite the presence of an even higher oral temperature and histories which were facsimiles of cases herein presented. Oral temperature rarely exceeded 99.8° F. but in three cases occasionally reached 100.2° F. Simultaneous recordings disclosed that at its daily peak, the oral was at the same level as or higher than the rectal by as much as 0.6 degree.

No constant relationship between mouth and rectal temperature could be established. Generally, oral was lower than rectal in the morning but equalled or exceeded the latter in the afternoon. Mouth temperature was usually between 97 and 98° F. at 7 a.m. and rose to its maximum peak at 3 p.m. Oral hyperthermia throughout the day was rarely exhibited for periods exceeding 48 hours. Complete remission of oral fever for one to two days was commonly noted but invariably followed by recurrence while under observation, with but one exception (case 5, table 2).

All patients had received one or more courses of the sulfonamides; a therapeutic test of emetine proved ineffectual in three. Tonsillectomy in three and removal of dental foci of infection were without benefit. Continuous bed-rest and mild sedation (phenobarbital) did not influence the course of 'fever.' Benzedrine sulfate was tolerated poorly by two subjects to whom it was administered to combat fatigue, and was discontinued after two days.

5. *Diagnosis.* Notwithstanding the oral hyperthermia, the maintenance of a normal rectal temperature is considered incompatible with the concept of fever on an infectious basis. The inability to confirm the presence of true fever, the normal laboratory studies, and the absence of significant physical

findings other than manifestations of autonomic lability strongly suggested that an anatomic basis for either the symptomatology or the pseudo-pyrexia was unlikely.

Many manifestations of neurosis, usually neurasthenic, or even psychosis may arise during the course of protracted fever, but these are, as a rule, transient and secondary to toxic insult. In patients of this series, however, a preponderance of neuropathic traits, and many of the symptoms for which they were being observed, had been present for many years prior to induction into the army. A history of vasomotor instability was obtained in 92 per cent evidenced by hyperhidrosis, palpitation on effort, easy fatigability, vertigo, and coldness of extremities, long antedating entry into military service. In 10 cases, these symptoms were sufficiently pronounced to warrant a primary diagnosis of neurocirculatory asthenia, typified by the following:

Case 13 (table 2). Pfc., aged 21, enuretic until 17 years, had always been underweight, 'nervous,' easily fatigued, subject to palpitation on slight exertion, and had noted perennial hyperhidrosis. He was inducted Oct. 15, 1943 and was admitted to a Station Hospital Nov. 2, 1943 complaining of sore throat, palpitation, cough and dyspnea. Physical examination was negative apart from mild tonsillitis, temperature 101.5° F. and pulse rate 125 p.m. Within 48 hours temperature had receded to 99°, but a daily rise to 99.8° was noted thereafter. He was transferred to a General Hospital Dec. 10, 1944 after various diagnostic procedures failed to reveal the cause of the fever. Blood counts, urinalyses, sedimentation index, basal metabolism, electrocardiogram, stools, spinal fluid, blood and throat cultures, non-protein nitrogen, sputum, gastric contents, prostatic smears, serological tests for syphilis, typhoid, tularemia, undulant fever and infectious mononucleosis; skin tests for tuberculosis, brucellosis and coccidioidomycosis, sternal marrow, allergy survey, chest and sinus roentgenograms, intravenous pyelogram and gastrointestinal series were normal. Glucose tolerance curve was somewhat flattened. Oral temperature continued to range between 98.2 and 99.8° F. Bed-rest, sulfathiazole, sedation, and finally tonsillectomy failed to influence the low-grade pyrexia. Following 250 days of hospitalization during which fever did not recede for periods beyond 36 hours, he was transferred to a general hospital with diagnosis 'fever of undetermined origin.' On admission patient appeared asthenic, weight 132 lbs. (height 67"). He stated that he had lost 'considerable' weight, but records proved his pre-induction weight to be 136 lbs. He complained of fever, chilly sensations, throbbing headache, palpitation, constant fatigue, anorexia, shooting pain in both groins, and precordial distress. Examination revealed nothing of note except for marked hyperhidrosis of palms, soles, and axillae with cold extremities, and considerable fluctuation of pulse rate during examination from 90 to 130 p.m. Rectal temperature during initial examination was 99.4° and oral 99.8° F. Four-hour determinations (simultaneous) for 10 days disclosed the following average daily recordings:

	<i>Oral</i>	<i>Rectal</i>
7 a.m.	97.6	98.0
11 a.m.	98.6	98.8
3 p.m.	99.4	99.4
7 p.m.	99.8	99.4
11 p.m.	99.4	99.2

On three occasions oral temperature, at its maximum daily peak, exceeded the rectal by 0.6 degree. The latter never rose beyond 99.6°. Cardiologist concurred in

the diagnosis of neurocirculatory asthenia, while psychiatrist found evidence of severe long-standing psychoneurosis, mixed type (neurasthenia and anxiety). Rectal temperature remained normal during his three-week stay at this hospital, but oral hyperthermia continued. As psychotherapy was not deemed beneficial in view of the chronicity of his symptoms, and in view of his meager military training (17 days), following repeated reassurance regarding the fever he was discharged from service. Four months later he reported that he was working on his father's farm and had no occasion to take his temperature or seek medical advice, but fatigue and nervousness persist.

Some cases were classified as psychoneurosis, mixed type, with anxiety the commonest component. It is emphasized that the longer the period of hospitalization, the more pronounced the evidence of neurosis. Indeed, the disparity between multitudinous complaints and meager clinical findings varied directly with the length of hospitalization. The preinduction history of this group is replete with neurotic trends and portends maladjustment to stress and strain of military life. Five were members of 'alerted' units when originally hospitalized while two had been evacuated from overseas, having been admitted to the hospital two weeks after arrival in the South Pacific. These are common factors bearing an important relationship to the progression of anxiety. Clear indication of long-standing autonomic dysfunction was present in all. Four soldiers exhibited conversion phenomena classically illustrated by the following:

Case 20 (table 2). Pvt., aged 28, a lawyer in civil life, had always been unaggressive, timid, self-conscious, dependent, and subject to phobias, palpitation, hyperhidrosis, vertigo, and easy fatigue since childhood. Despite one year of service with his Signal Corps unit he had received no promotions. Although he felt ill at ease due to necessity of obeying orders given by men he considered his intellectual inferiors, he stated that he shunned the responsibilities entailed by promotion. Two weeks after arriving in Australia he developed herpes zoster involving the right mid-abdomen and trunk and was admitted to a general hospital Nov. 1, 1943 with temperature 101° F. Temperature dropped to 100° in five days and rash disappeared in three weeks but his afternoon oral temperature rose daily to 99.8° F. Neurological examination was negative. Spinal puncture Nov. 22, 1943 revealed essentially normal fluid except for slight elevation of globulin (42 mg./100 c.c.). On the following day he complained of severe pain in his lumbar spine and weakness of his right leg. Within a week he developed an ascending weakness involving the right upper and lower extremities and right side of his face. A mask-like facies was noted. Deep reflexes were questionably diminished on the right, but all superficial reflexes were normal. A diagnosis of 'encephalitis' was at first entertained but later altered to 'Guillain-Barré syndrome.' Observation continued for four months, the loss of muscle function becoming gradually more marked, while daily fluctuation of oral temperature to 99.8° showed no recession. Because of failure to improve, he was evacuated as a litter patient to a general hospital April 4, 1944 with the diagnosis 'fever of undetermined origin, probably Guillain-Barré syndrome.' He was admitted by error to the General Medical section because of the primary diagnosis of obscure fever, and presented an apathetic picture, having lost 15 lbs. after five months in bed. Examination revealed mask-like facies, marked hyperhidrosis of hands and feet, right hemiparesis, normal reflexes, and a variable hypesthesia involving the entire right half of the body extending to the midline. The diagnosis of hysteria was considered most plausible in view of the normal reflexes and bizarre sensory disturbance. At initial examination oral temperature was 99.8° F.

and rectal 99.2° F. Four-hourly determinations proved that hyperthermia existed only orally. Neurologist confirmed the diagnosis of hysteria. Following appropriate suggestion, 7½ gr. sodium amytal were administered intravenously and patient rose from his bed, walked across the room and was able to swing his right arm for the first time in 10 weeks. On the following day he was able to feed himself and walk along the hall unaided. Restoration of full muscle strength was complete within one week and he was transferred to the Reconditioning Facility in the hope that he might eventually be returned to duty, having been assured an assignment consistent with his educational background. After three weeks, however, he stated that he 'couldn't make the grade' as he realized he was a complete failure in the army. Observations of both rectal and oral temperature following loss of conversion symptoms failed to indicate any change from their previous levels. Neurological examination was completely normal, and mask-like facies was no longer noted. Psychiatrist diagnosed 'conversion hysteria in an inadequate individual.' Lumbar puncture was not repeated to forestall the precipitation of further hysterical phenomena. He was discharged from the army and no further communication was received from him.

Case 3 (table 2). Pvt., aged 23, with eight months of service, developed sore throat and fever at a port of embarkation Dec. 22, 1943 and was admitted to a Station Hospital where 'acute tonsillitis' was diagnosed. Temperature was 103° F. on admission but receded to 99.2° F. in 72 hours. A low-grade irregular oral fever was noted thereafter, with daily rise to a maximum of 100° F. from a usually normal morning level. He was transferred to a General Hospital Jan. 15, 1944 for further investigation. Comprehensive laboratory studies failed to reveal an anatomic basis for the fever. Tonsillectomy and therapeutic trials of sulfathiazole and emetine were without benefit. Although his initial complaints were minimal, he developed an indefinite and ever-progressive pattern of symptoms including increasing fatigue, anorexia, headaches, chills and fever, pain in the middorsal spine radiating anteriorly and up his neck, precordial distress, and numbness of the right shoulder and arm. After 17 weeks of daily temperature elevation, he was transferred to a general hospital with the diagnosis 'fever of undetermined origin.' Examination on admission revealed excellent nutrition despite complaint of anorexia. Hypesthesia of the right arm to the elbow and of the right chest wall with sharp termination at the level of the elbow, not conforming to normal nerve distribution, was present. Moderate hyperhidrosis, tachycardia, and coarse tremor were noted. Simultaneous oral and rectal temperature determinations over a 10-day period revealed oral hyperthermia with normal rectal temperature. Patient revealed that he had always been restless, self-conscious, and tense. He had always been aware of palpitation and profound blushing when confronted with strangers. He had always been excused from physical training during his school career owing to 'rapid heart rate' and 'heart pain on exertion.' He had never been aware of fever until this period of hospitalization. Convalescence from 'colds' in civilian life had always been prolonged because of fatigue. Cardiologist at this hospital confirmed presence of a normal heart with neuro-circulatory asthenia. Psychiatric diagnosis was 'psychoneurosis, anxiety and conversion.' Following repeated reassurance regarding the nature of his symptoms and oral fever, he was transferred to the Reconditioning Facility for six weeks, temperature recordings having been discontinued. Pain in the spine and numbness of arm and chest disappeared gradually without use of narco-synthesis. Convalescence was uneventful and he was returned to sedentary duties within the continental limits of United States. Studies of temperature were made for four days prior to release from this hospital and both rectal and oral temperatures were normal throughout the day. Communication from him after six months reported that he was doing clerical work at a fixed installation and that he had no occasion to seek medical advice since leaving the hospital although he felt tired throughout the day. He no longer experienced sensation of 'chills and fever' but had not rechecked either oral or rectal temperature.

It is considered that prolonged hospitalization is an important contributory factor in the progression of anxiety in many of this group. The constant stressing of temperature level, bed-side reference to fever of obscure origin, and numerous laboratory studies with inconclusive results instill the patient with the belief that he is suffering from a rare illness which has completely baffled his examiners. In suggestible individuals, this cannot fail to give rise to considerable apprehension and anxiety with the concomitant development of a wide variety of psychosomatic manifestations. This is illustrated by the following:

Case 17 (table 2). Pvt., aged 28, a radio school student with seven months of service, had always been active, aggressive, ambitious, and egocentric. He was admitted to a Station Hospital Dec. 10, 1943 because of sore throat and fever of 103° F. Temperature fell to 99.4° F. after 72 hours and he had no complaints but because of a daily rise of oral temperature he was retained in the hospital despite his protests. Following one month of investigation which failed to disclose a cause for fever he was returned to duty with instructions to report to the dispensary for daily temperature observation at 4 p.m. Because the latter was noted to be 99.8° on several occasions he was readmitted to the hospital for three weeks where further studies failed to uncover an infective focus. As he had no symptoms, he was again returned to duty. Owing to the inconvenience entailed by daily visits to the dispensary, he purchased a thermometer and recorded his temperature several times daily. About Feb. 15, 1944 he began to experience 'chills and fever' at approximately 6 p.m. each day, at which time his oral temperature reached a peak of 99.6° F. Because of this, he retired at 5:30 p.m. nightly to 'await his chill,' which would invariably leave him completely fatigued. On March 1, 1944 he requested readmission to the hospital because of increasing fatigue, fever, headache, anorexia and insomnia. After a protracted investigation, he was transferred to a general hospital April 7, 1944 with the diagnosis 'fever of undetermined origin.' Physical examination was entirely negative. Patient was observed taking his own temperature frequently during the day and this practice was ordered discontinued. Our own studies over a 14-day period confirmed the presence of oral hyperthermia with consistently normal rectal temperature. Afebrile periods up to 36 hours were noted on three occasions. It required considerable reassurance to convince him that he had neither an infectious fever nor underlying organic disease. This was accomplished in part by permitting him to take his own rectal temperature recordings. His daily 'chill' occurred even during afebrile periods. Amphetamine sulfate, administered in 10 mg. dose on two occasions, produced tremor, palpitation, tachycardia (102 p.m.) and profuse perspiration with an increase in oral temperature from 98.4° and 98.6° respectively, to 99.2° F. in one hour. A definite history of autonomic instability or neurotic traits prior to his present illness could not be obtained. Following three weeks of graduated exercise on the Reconditioning Facility, during which temperature studies were discontinued, all symptoms except fatigue disappeared. Maximal mouth temperature was 99.2° with 99.4° by rectum during a four-day period of observation, after the above regime. He was returned to duty with the diagnosis 'observation, no disease found.' Five months later he reported that he was asymptomatic and that his mouth temperature had been repeatedly under 99°.

Thus, it is possible that a transient tension state with attending hypochondriasis had been created in this self-centered soldier by the repeated suggestion of fever due to an obscure smoldering disease, although the oral hyperthermia was possibly the result of autonomic instability following a febrile disease (tonsillitis).

6. *Management.* Four-hourly temperature determinations for 10 days were considered adequate to rule out the possibility of true pyrexia since none had been afebrile longer than two days prior to admission to this hospital. Thereafter only rectal recordings were made twice daily to impress upon them that they were not 'fever problems,' as these patients are prone to be 'thermometer-conscious.' When an anatomic basis for their symptoms had been clearly eliminated, detailed psychiatric and cardiovascular studies were instituted, patients remaining on the general medical section until final evaluation had been formulated. Those transferred to the Reconditioning Facility were recalled to the Medical Service for a final period of observation preparatory to return to duty or separation from service if they failed to qualify for even sedentary duty.

7. *Disposition and follow-up* (table 2). During the period covered by this survey, group psychotherapy had not yet been given general application in the reconditioning program, and it is possible that this form of therapy might have yielded a higher salvage rate. Furthermore, the majority of those soldiers returned to duty gave evidence of poor adjustment to military routine, portending future difficulties and hospitalizations.

Reports were received in three to six months from nine of those discharged from the army. All were engaged in civilian occupations and had required no subsequent medical care. Three state that their oral temperature is normal; six omit mention of the latter. All comment vaguely regarding 'nervousness.'

Ten were returned to 'limited service' despite persistence of many of their symptoms present on admission. Oral temperature had reverted to normal in but one (case 3). Two were discharged from the army within two months, both soldiers reporting that they had been reassigned to duties which were too strenuous. Four others were traced three to six months after release from this hospital. Two stated they felt well and did not believe they had fever, while two reported they were 'no better.' Four of this group have not been heard from.

Communication was received from one of the two men returned to full duty (case 17) with a wholly favorable course.

No definite conclusions are warranted from these meager returns, and it is believed that the majority of those who reported the absence of oral fever were guided subjectively rather than by thermometer readings. In general, it appears that those patients who had secured release from service had fewer symptoms than those returned to duty, while none of either group, with whom contact had been established, developed progression of symptoms or physical deterioration.

DISCUSSION

Fever is almost invariably regarded as indicative of organic disease. Wechsler³ categorically states that fever is never hysterical. Nevertheless Eichelberg,⁴ Potosky,⁵ Deutsch⁶ and others have advanced convincing proof

that fever may have a hysterical origin and recede under hypnosis. In their case reports, however, elevation of rectal temperature was always noted. The cases herein described never presented a rectal temperature above normal while under observation at this hospital. In view of the fact that the height of the oral temperature persisted at the same level as at previous hospitals, it is reasonable to assume that a normal rectal reading had been present for some period prior to admission here.

In explaining the cause of this temperature paradox it must be assumed that in addition to an increase in oral circulation there must be a variation from the normal distribution of blood in the oral and rectal tissues.

That irradiation of impulses from higher centers may produce profound effects on peripheral circulation is evidenced by such phenomena as syncope, pallor, blushing, and erection. Thus, psychic stimuli exert an influence upon the vascular mechanisms and reciprocal relations which exist between such vascular beds as the muscular and cutaneous tissues, the splanchnics and skin.

Following a febrile disease, the heat regulating mechanism is notoriously unstable and reacts sharply to both emotional and physical stimuli. Thus in psycholabile individuals, temperature rise following infection is not necessarily the result of psychic injury but may reflect the increased lability of the heat-regulatory mechanism acquired through organic disease.

It is conceivable that following an initiating febrile episode in an individual with autonomic instability, the heat regulating apparatus acquires a lability which may persist for long periods as a result of repeated or continuous situational and environmental stress. In some subjects, such psychic stimuli may produce an alteration of the usual reciprocal relation between vascular beds resulting in increase of oral circulation through selective sympathetic stimulation. The imposition of a strong element of suggestion will not alone prolong this response but, in a suggestible subject, may result in actual somatic sensation of 'fever.'

However, although it would appear that an infection resulting in authentic pyrexia, even though of short duration, initiated this response in 88 per cent of this series, the possibility must be entertained that oral hyperthermia antedated the infection which resulted in hospitalization. This is further suggested by the accidental discovery of 'oral fever' of a similar type in the three cases in this series who were being observed for non-infectious disorders, but who displayed considerable psycholability. It would bear out the observations of Friedman⁷ who noted episodic oral hyperthermia in 36 per cent of 30 cases of neurocirculatory asthenia without known antecedent infection. In four cases there was neither subsidence nor progression during an observation period of 110 days. Correlating rectal temperatures were not reported in his study, but the cases surveyed appear to be facsimiles of those herein presented.

Nevertheless, that an antecedent stimulus, usually a febrile episode of infectious origin is an important factor in the elaboration of this syndrome is suggested by the absence of thermal abnormalities in the patients observed

on the neuro-psychiatric wards at this hospital, and in whom autonomic instability is frequently associated with anxiety. Cases of oral hyperthermia have been discovered among patients referred to this department from other sections of the hospital for evaluation of persistent low-grade oral fever. These oral hyperthermics invariably emanated from the contagion and surgical wards, and in the latter instance, temperature elevation appeared to have originated post-operatively.

Finally, it must be considered that a small percentage of individuals may normally exhibit oral hyperthermia without relation to infection or to vasomotor or psychic instability.

COMMENT

In large medical installations where temperature is estimated almost exclusively per os, due to the facility of this method, elevations, unless attended by unequivocal signs of infection should be controlled by rectal recordings. Where the latter remain consistently normal, the patient may be considered afebrile. This does not imply that associated symptoms be disregarded, but that careful clinical consideration be given before instituting a prolonged hospital regime and a medley of diagnostic procedures. The associated psychic stress may so harass a patient as to prolong hyperthermia and produce symptoms through pain and fear. In the management of patients with this syndrome the best weapon in allaying apprehension and engendering confidence is an attitude of the clinician indicating complete familiarity with its manifestations. The significance of elevated mouth temperature should be minimized while stressing the normal rectal level as being incompatible with fever on an organic basis. The practice of taking frequent oral temperature recordings should be discouraged when this paradox has been uncovered.

The term 'fever' is not ordinarily applied to the hyperthermia in the tissues involved by localized inflammation such as a furuncle or phlebitis. It is thus suggested that the syndrome herein presented of oral fever with normal rectal temperature be designated as 'essential oral hyperthermia.' The designation 'fever of undetermined origin' should be relegated to such cases which display elevation of temperature of the entire body rather than selective areas. While clinical impressions thus far strongly indicate that in the overwhelming majority of cases it stems from an inherent vasomotor instability, study of a larger series with adequate controls over a long period is desirable before it can be conclusively established to be solely on a functional basis.

SUMMARY AND CONCLUSIONS

1. Oral temperature may be elevated to levels generally regarded as abnormal, and exceed coexisting rectal temperature for prolonged periods without demonstrable organic disease. A series of 25 cases exhibiting this thermal paradox is presented.

2. Although the pathogenesis of this condition is not clearly established the weight of clinical evidence indicates that in the large majority of cases this response is initiated by an antecedent infection in psycholabile individuals which renders the heat regulating mechanism unstable. A reversal of the usual reciprocal mechanism existing between vascular beds by sympathetic stimulation from higher centers may produce increase of oral circulation.

3. Prolongation of this response and the elaboration of somatic sensation of fever may result from apprehension engendered by prolonged hospitalization, and the repeated suggestion to the patient of an underlying obscure disease.

4. The possibility of oral hyperthermia preëxisting the infection, in subjects with vasomotor instability or even being exhibited by normals is considered.

5. The demonstration of elevated oral temperature without associated evidence of infection should be invariably controlled by rectal temperature determinations. If the latter remain consistently normal, prolonged hospitalization and laboratory search for cryptogenic sepsis is unwarranted.

6. The term 'fever of undetermined origin' is misleading and is not applicable to localized temperature elevations.

7. "Essential oral hyperthermia" is suggested as a more accurate designation of this benign thermal disturbance.

8. An arbitrary level of 99° F. as the maximum limit of normal oral temperature is not valid.

BIBLIOGRAPHY

1. WRIGHT, A. I.: Textbook of Physiology, 1938, W. B. Saunders Co., Philadelphia.
2. ROWNTREE, L. G., and KINTNER, ARTHUR R.: Long-continued, low-grade idiopathic fever, Trans. Assoc. Am. Phys., 1934, xlvii, 60-69.
3. WECHSLER, I. S.: Cecil's Text-book of Medicine, 1941, W. B. Saunders Co., Philadelphia, p. 1654.
4. EICHELBERG, P.: Durch Hypnose erzeugtes "Hysterisches Fieber," Deutsch. Ztschr. f. Nervenhe., 1921, lxxviii-lxix, 352-356.
5. POTOSKY, CARL: Psychogenese und Psychotherapie von Organsymptomen beim Kinde. In: Q. SCHWARTZ, Psychogenese und Psychotherapie körperlicher Symptome, 1925, Springer, Wien, p. 385-424.
6. DEUTSCH, F.: Das psychogene Fieber, Med. Klin., 1926, xxii, 1213-1215.
7. FRIEDMAN, MEYER: Etiology and pathogenesis of neuro-circulatory asthenia, War Med., 1944, vi, 221-227.

THE NEPHROTIC PHASE: ITS FREQUENCY OF OCCURRENCE AND ITS DIFFERENTIAL DIAGNOSTIC VALUE IN DETERMINING THE NATURE OF THE RENAL LESION IN 120 PATIENTS WHO DIED OF RENAL FAILURE*

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INTRODUCTION

THE term "nephrotic phase" is used to describe a syndrome occurring during the course of chronic glomerulonephritis and characterized by albuminuria, hypoproteinemia, hypercholesterolemia and edema. In general, these features have served as the criteria for diagnosis.^{1,2} The degrees of hypoproteinemia, proteinuria, edema and lipemia necessary for the diagnosis have not been clearly defined.

There is agreement over the occurrence of the nephrotic phase in particular types of renal diseases which terminate in renal failure. Baehr³ noted that "every case of glomerulonephritis has a nephrotic element." Christian⁴ agrees with this opinion. The rarity of the nephrotic phase in arteriolar nephrosclerosis is noted by Loeb⁵ who states that, "The nephrotic syndrome with marked depression of the albumin-globulin ratio also serves as a distinguishing feature since it does not occur in arteriolar nephrosclerosis." Weiss and Parker⁶ and Fishberg⁷ mention the infrequency of generalized edema during the course of pyelonephritis in the absence of cardiac failure. Recently, Mansfield, Mallory and Ellis¹⁶ have again called attention to the absence of the nephrotic phase in a series of patients with arteriolar nephrosclerosis and pyelonephritis. It seems clear from the opinions expressed above that the nephrotic phase is a common feature of chronic glomerulonephritis and, if it occurs at all, a rare phenomenon in arteriolar nephrosclerosis and chronic pyelonephritis. However, the factual data to support this opinion are scanty in the medical literature.

The present study, therefore, was undertaken to determine the frequency of the nephrotic phase in a large series of patients dying of renal failure caused by chronic glomerulonephritis, arteriolar nephrosclerosis and chronic pyelonephritis. The differential diagnostic value of this syndrome would then be apparent if it were found to occur exclusively in the course of only one of these entities.

DATA

The case histories of 120 patients dying of renal failure were reviewed. These consisted of 50 instances of chronic glomerulonephritis, 50 of arterio-

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From the Research Service, First (Columbia) Division, Goldwater Memorial Hospital, Department of Hospitals, and the College of Physicians and Surgeons, Columbia University, New York City.

lar nephrosclerosis and 20 of chronic pyelonephritis. Autopsy was conducted in each instance. One hundred and six patients had been observed at the Presbyterian Hospital and 14 patients had been observed at the First (Columbia) Research Division of the Goldwater Memorial Hospital. The diagnosis of renal failure prior to death was made on the basis of the clinical picture and diminished or diminishing renal function as determined by one or more of the usual tests. Although the degree of renal failure in these patients varied over a wide range during the period of observation, no patient was accepted for this study unless the evidence of renal insufficiency was obvious.

The postmortem examinations were done by members of the Department of Pathology of the College of Physicians and Surgeons of Columbia University. The interpretation of the pathologist is accepted as the final diagnosis in each case, although there were differences of opinion between the clinician and pathologist in a few instances. When the 120 consecutive case histories were found to conform to (a) the pathological diagnosis of either chronic glomerulonephritis, arteriolar nephrosclerosis or chronic pyelonephritis, and (b) the presence of a period of renal insufficiency prior to death, a study of each chart was made to determine any evidence which would indicate the presence of the nephrotic phase during the period of clinical observation. This evidence is now presented in reference to each finding.

Those patients were considered in a nephrotic phase who showed albuminuria, hypoproteinemia, hypercholesterolemia and edema.

SERUM PROTEINS

A comparison of the serum protein values in the three groups of patients is shown in table 1. In those patients with chronic glomerulonephritis there were frequent determinations made throughout the period of observation.

TABLE I

Serum Protein Values During the Clinical Course of 120 Patients Dying of Renal Failure

	Chronic Glomerulonephritis	Arteriolar- nephrosclerosis	Chronic Pyelonephritis
Total number of patients	50	50	20
Number of patients with serum protein determinations	45	42	11
Number of patients with normal serum protein levels	9	25	5
Number of patients with serum proteins below 6 gm. %	36	17	6
Number of patients with serum proteins below 5 gm. %	22	2	3
Number of patients with serum proteins below 6 gm. % in absence of cardiac failure or malnutrition	26*	1	1

* Two of these determinations occurred in patients not having nephrotic phase. The total serum protein level was 5.9 per cent in one patient and 5.3 per cent in the other.

In the other two groups the number of determinations per patient was comparatively small. This was due to the fact that a decrease in the serum protein level in the latter two groups was seldom expected. The table indicates that roughly four-fifths of the patients with chronic glomerulonephritis had a decreased serum protein value whereas about two-fifths of those with arteriolar nephrosclerosis or pyelonephritis showed a value below normal. The degree of alteration was much greater in those patients having chronic glomerulonephritis.

These data corroborate the findings of many others. It has been previously noted by Peters and Van Slyke,⁸ and Fishberg⁷ that hypoproteinemia is a frequent finding at some time during the course of chronic glomerulonephritis. On the other hand Linder, Lundsgaard and Van Slyke,⁹ Peters,¹⁰ Van Slyke, Stillman, Möller and his associates¹¹ have shown that patients with arteriolar nephrosclerosis have normal serum proteins if nutrition is adequate and cardiac failure is absent.

SERUM CHOLESTEROL

A comparison of the serum cholesterol values in the three groups of patients is shown in table 2.

TABLE II

Serum Cholesterol Levels During the Clinical Course of 120 Patients Dying of Renal Failure

	Chronic Glomerulonephritis	Arteriolar- nephrosclerosis	Chronic Pyelonephritis
Total number of patients	50	50	20
Number of patients with cholesterol determinations	36	15	9
Number of patients with cholesterol over 300 mg. %	26	3	1
Number of patients with cholesterol below 300 mg. %	10	12	8

Although the determinations of serum cholesterol were limited in number, the data in the table suggest that hypercholesterolemia is a far more frequent finding in patients having chronic glomerulonephritis than in the other two groups of patients. These data are consistent with the opinion expressed by other workers. Peters and Van Slyke⁸ state that serum lipids as well as serum cholesterol are elevated in nephrotic types of glomerulonephritis and less commonly in non-nephrotic types. Steiner and Domanski¹⁵ found that serum cholesterol levels exceeded 300 mg. per cent in 30 of 54 patients having chronic glomerulonephritis. Bloor,¹² Denis¹³ and Page, Kirk and Van Slyke¹⁴ have shown values within normal limits in patients with arteriolar nephrosclerosis.

PROTEINURIA

The incidence of severe proteinuria occurring during the course of clinical observation in the three groups of patients is shown in table 3. Differentiation is made between proteinuria due to renal disease alone and pro-

TABLE III
Incidence of Marked Proteinuria During the Clinical Course of 120 Patients
Dying of Renal Failure

	No. of Patients	4+ Proteinuria*	Heart Failure at Time of 4+ Proteinuria
Chronic glomerulonephritis	50	40	10
Nephrotic phase	27†	25	4
Non-nephrotic phase	23	15	6
Arteriolar nephrosclerosis	50	16	15
Chronic pyelonephritis	20	3	1

* This refers to a period during the patients' observation when consecutive findings of 4+ proteinuria were present.

† 24 patients who had nephrotic phase during the period of observation; 3 patients who had a history of nephrotic phase before the period of observation.

teinuria observed when complicated by heart failure. It is seen from this table that: (1) marked proteinuria is more frequently found in chronic glomerulonephritis than in arteriolar nephrosclerosis or chronic pyelonephritis, (2) when the proteinuria of the nephrotic phase occurred, it was usually unassociated with cardiac failure during specified periods of observation, (3) when severe proteinuria occurred in arteriolar nephrosclerosis there generally was associated cardiac failure. The urine proteins were determined by the heat and acetic acid test. Peters and Van Slyke⁸ have observed that, "Among patients with chronic nephritis those with degenerative nephritis or the chronic active stage of hemorrhagic nephritis excrete the largest amounts of protein. . . . In the nephrosclerotic type of disease, the quantity of protein in the urine is usually small, sometimes almost undemonstrable." Recently Mansfield, Mallory and Ellis¹⁶ have made similar observations.

EDEMA

The incidence of the history of edema occurring in the three groups of patients is summarized in table 4. It may be seen from the table that: (1) in

TABLE IV
Presence of Edema During the Clinical Course of 120 Patients Dying of Renal Failure

	Total	Edema	Anasarca	At Time of Edema	
				Heart Failure	Mal-nutrition
Chronic glomerulonephritis	50	37	13	10	7
Nephrotic phase	27*	26	12	4	2
Non-nephrotic phase	23	11	1†	6	5
Arteriolar nephrosclerosis	50	27	2†	21	6
Chronic pyelonephritis	20	12‡	0	6	4

* 24 patients observed with nephrotic phase as defined in this paper. 3 patients had substantiated histories of nephrotic phase.

† Heart failure cause of anasarca.

‡ One patient had cirrhosis of the liver and low serum proteins. One patient had edema from forced saline therapy.

patients having the nephrotic phase of chronic glomerulonephritis, edema is frequently observed in the absence of cardiac failure or malnutrition, (2) when edema is present in arteriolar nephrosclerosis or chronic pyelonephritis, heart failure or malnutrition is frequently present, (3) anasarca occurred chiefly in the patients having the nephrotic phase. Twelve of 27 patients having the nephrotic phase of chronic glomerulonephritis had anasarca, the remaining 15 patients having only moderate or slight edema. In this latter group the serum protein level, the hypercholesterolemia, and marked albuminuria favored the diagnosis of the nephrotic phase.

TABLE V
Incidence of the Nephrotic Phase during the Clinical Course of 120 Patients
Dying of Renal Failure

	Total Cases	With Nephrotic Phase	% With Nephrotic Phase
Chronic glomerulonephritis	50	27	54
Arteriolar nephrosclerosis	50	? 1	? 2
Chronic pyelonephritis	20	? 1	? 5

DISCUSSION

It is shown in table 5 that 54 per cent of the patients with chronic glomerulonephritis had a typical nephrotic phase. Forty-eight per cent exhibited the quadrad of edema, hypoproteinemia, marked proteinuria and hypercholesterolemia during the period of clinical observation. Six per cent had a history of the nephrotic phase in the past without a history of protein starvation or cardiac failure. In another 20 per cent, one or more of the classical signs were seen; namely, edema, hypoproteinemia, cholesterolemia or heavy proteinuria or combinations of these changes. These alterations could not be explained on the basis of malnutrition, cardiac failure or another disease process producing an increase in the serum cholesterol level. These findings, with a few exceptions, could not be duplicated in the group of patients with renal failure due to nephrosclerosis or pyelonephritis. In only 26 per cent of the patients with chronic glomerulonephritis was there a complete absence of the findings usually associated with the diagnosis of the nephrotic phase. The period of clinical observation in these cases was shorter than that in the nephrotic phase group. In 21 of the 27 patients having the nephrotic phase, the period of observation was for one or more years. However, of the 23 patients not having the nephrotic phase, there were only six patients with a follow-up period of one or more years. Thus there is the possibility of the nephrotic phase having occurred in certain of the latter patients at some time before the period of observation.

In a parallel study, it was found that of 11 patients with chronic glomerulonephritis who were observed for a long period at the Columbia Research Service of the Goldwater Memorial Hospital, 10 exhibited classical findings of the nephrotic phase. The remaining patient, who was shown to

have intercapillary glomerulonephritis at autopsy, was said to have had a mild nephrotic phase prior to admission. However, he manifested no edema during a one-year period with us and his serum albumin value was never below 3.8 gm. per 100 c.c. The degree of proteinuria was four plus. The serum cholesterol level varied between 377 and 610 mg. per cent, with a mean of 479 mg. per cent. The basal metabolism was normal and there was no evidence of diabetes mellitus.

During this study the question of a repetitive nephrotic phase was raised. In the present series of case histories no evidence was found of the nephrotic phase occurring more than once during the course of glomerulonephritis. The duration of the nephrotic phase ranged from two months to five years. The average duration was 22.5 months.

In the series of 50 patients who died of arteriolar nephrosclerosis, there is one patient having the nephrotic phase (table 5). Although there is no doubt as to the presence of the nephrotic phase, there is doubt as to the diagnosis of the renal disease in this patient. Description of the pathological changes in this case history indicated that the findings were of a borderline character which are difficult to classify. There is only one patient in the pyelonephritis series with findings suggestive of the nephrotic phase. On closer analysis these findings are not exactly in keeping with our definition, for the marked proteinuria was not present at the same time as the hypoproteinemia and hypercholesterolemia. This study thus confirms the opinion that the nephrotic phase is a frequent feature of chronic glomerulonephritis and a rare phenomenon in arteriolar nephrosclerosis and chronic pyelonephritis. The differential diagnostic value of the nephrotic phase is thus apparent, for once established, it helps to identify the renal lesion as that of chronic glomerulonephritis.

CONCLUSIONS

1. The nephrotic phase is defined as the concomitant occurrence of edema, hypoproteinemia, hypercholesterolemia and a marked proteinuria. Difficulty is encountered in establishing this diagnosis in the presence of cardiac failure and severe malnutrition.

2. The opinion is confirmed that the nephrotic phase is a frequent finding during the course of chronic glomerulonephritis and a rare phenomenon during the course of chronic pyelonephritis or arteriolar nephrosclerosis. The presence of the nephrotic phase is therefore a useful differential diagnostic factor in the diagnosis of the cause of renal failure.

3. The nephrotic phase may extend over a number of years. The average duration in these patients was 22.5 months.

4. No evidence of a repetitive nephrotic phase was observed in this series of patients.

We are indebted to members of the Department of Pathology of the College of Physicians and Surgeons for the use of their records.

BIBLIOGRAPHY

1. LEITER, L.: Nephrosis, *Medicine*, 1931, x, 221-225.
2. ATCHLEY, D. W.: The nephroses, *Textbook of Medicine*, Cecil, 1943, 6th edit., W. B. Saunders Co., Philadelphia, 924-925.
3. BAEHR, G.: Discussion of "Nephrosis with glomerulonephritis," (case report) Margaret Worwick. Presented at Scientific Proceedings of the Twenty-Eighth annual meeting of the American Association of Pathologists and Bacteriologists, *Am. Jr. Path.*, 1928, iv, 632.
4. CHRISTIAN, H. A.: Nephrosis: A critique, *Jr. Am. Med. Assoc.*, 1929, xciii, 23-25.
5. LOEB, R. F.: Nephritis, *Textbook of Medicine*, Cecil, 6th Ed., 1943, W. B. Saunders, Philadelphia, p. 903-924.
6. WEISS, S., and PARKER, F., JR.: Pyelonephritis: Its relation to vascular lesions and to arterial hypertension, *Medicine*, 1939, xviii, 221-315.
7. FISHBERG, A. M.: Hypertension and nephritis, 1939, Lea and Febiger, Philadelphia.
8. PETERS, J. P., and VAN SLYKE, D. D.: Quantitative Clinical Chemistry. Interpretations, 1935, Williams and Wilkins, Baltimore.
9. LINDER, G. C., LUNDGAARD, C., and VAN SLYKE, D. D.: The concentration of the plasma proteins in nephritis, *Jr. Exper. Med.*, 1924, xxxix, 887-955.
10. PETERS, J. P., BRUCKMAN, F. S., EISENMAN, A. J., HALD, P. M., and WAKEMAN, A. M.: The plasma proteins in relation to blood hydration. VII. A note on the proteins in acute nephritis, *Jr. Clin. Invest.*, 1932, xi, 97-102.
PAYNE, S. A., and PETERS, J. P.: The plasma proteins in relation to blood hydration. VIII. Serum proteins in heart disease, *Jr. Clin. Invest.*, 1932, xi, 103-112.
PETERS, J. P., BRUCKMAN, F. S., EISENMAN, A. J., HALD, P. M., and WAKEMAN, A. M.: The plasma proteins in relation to blood hydration. IX. Serum proteins in the terminal stages of renal disease, *Jr. Clin. Invest.*, 1932, xi, 113-122.
11. VAN SLYKE, D. D., STILLMAN, E., MÖLLER, E., EHRLICH, W., MCINTOSH, J. F., LEITER, L., MACKAY, E. M., HANNON, R. R., MOORE, N. S., and JOHNSTON, C.: Observations on the courses of different types of Bright's disease, and on the resultant changes in renal anatomy, *Medicine*, 1930, ix, 257-386.
12. BLOOR, W. R.: The distribution of the lipoids ("fats") in human blood, *Jr. Biol. Chem.*, 1916, xxv, 577-599.
13. DENIS, W.: Cholesterol in human blood under pathological conditions, *Jr. Biol. Chem.*, 1917, xxix, 93-110.
14. PAGE, I. H., KIRK, E., and VAN SLYKE, D. D.: Plasma lipids in essential hypertension, *Jr. Clin. Invest.*, 1936, xv, 109-113.
15. STEINER, A., and DOMANSKI, B.: Serum cholesterol and atherosclerosis in chronic glomerulonephritis, *Am. Jr. Med. Sci.*, 1942, cciv, 79-84.
16. MANSFIELD, J. S., MALLORY, G. K., and ELLIS, L. B.: The differential diagnosis of chronic Bright's disease, *New England Jr. Med.*, 1943, ccxxix, 387-395.

MEDICOLEGAL PROBLEMS IN DISTINGUISHING ACCIDENT FROM SUICIDE *

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I

INTRODUCTORY †

SUBSTANTIAL rights, duties, and penalties created by statute, contract or the common law and affecting life, liberty, and property often depend upon whether a death was caused or hastened by disease, accident, suicide or homicide or some combination of these causes. In the investigation of any sudden death one should consider all possibilities, and never, at the outset, arbitrarily limit the scope of the inquiry.¹ Appearances mislead and deceive quite as often in medicolegal investigations as in clinical medicine, and in the former there are additional complicating factors: purposeful simulation to hide crime or obtain money, and the fact that ultimately the real cause of death may be determined by a jury, administrative tribunal or court of law.

With these preliminary admonitions in mind, it is usually, but not always, possible to limit an inquiry in any one case to one of these four groups: (1) disease or accident, (2) accident or suicide, (3) accident or homicide, and (4) suicide or homicide. This paper is confined to the second class of cases.

Suicide is voluntary, willful self-destruction, the act of designedly destroying one's own life. A word of caution and exclusion: at law a suicide while insane is an accident and so also is an unprovoked homicide.² No attempt will be made here to distinguish between sane and insane suicides, thus limiting the discussion to distinctions between accidents and suicides, as those terms are commonly understood and defined.

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† Well-known and authoritative general sources, both legal and medical, are listed at the end of the paper under Additional References. Footnotes giving the author's last name with a page citation will refer the reader to the Additional References for the title, edition, year of publication, and publisher.

¹ Most texts on medical jurisprudence have introductory chapters giving good advice concerning the investigation which should be conducted at the scene of violence and upon postmortem examination.

² Cornelius, pp. 52-62. Yet if Lothario should disregard threats and call unarmed upon the irate husband, a jury might call it suicide! *Central Nat. Bank v. Genrl. Amer. Life Ins. Co.* (C.C.A. 6, Ohio, unreported) 11 CCH Life Cases 241, s.c. 105 F. (2d) 878 (1939), s.c. 136 F. (2d) 821 (1943).

II

SUBSTANTIVE LAW—HOW THE ISSUE ARISES

A

HISTORICAL. MISCELLANEOUS PROBLEMS AT CRIMINAL AND CIVIL LAW

1. *At Criminal Law*

Until a modern and enlightened social philosophy fostered insurance for accidental injuries or death arising at work or elsewhere, suicide presented very few problems except those which concerned the King and the Church, criminal and ecclesiastical law. Their attitude of aversion and condemnation left a very definite impression upon the common law, although in modern times a cynical civilization which has created a richer and more desirable life has, paradoxically, relaxed many restraints, and, in fact, created a few more incentives for the voluntary passage to "the undiscovered country from whose bourn no traveler returns."

In ancient times suicide was not frowned upon with disfavor by the Church.³ Neither Moses nor Christ spoke of it. When the deed was mentioned it was detailed as a historical fact without condemnation. It was not a crime except when committed by soldiers who thereby weakened the army and encouraged cowardice in battle.

During the Middle Ages and until only a few centuries ago suicide was considered an offense so heinous in England that the law pursued it after death, and to punish it inflicted degradation upon the body of the deceased. A stake was driven through the body and it was buried in the public highway. All of the deceased's estate was forfeited to the crown, and his soul and family lost many ecclesiastical solaces and beneficences. The sternness of some of these penalties was ameliorated in 1823 when burial without Christian rites was permitted in any parish graveyard between the hours of 9 and 12 at night. An Act of Parliament passed during the reign of Henry III providing for confiscation of the property of a suicide was not repealed until 1870. By an Act passed in 1882 all restrictions upon burials of suicides were finally lifted, except that Christian rites could not be conducted unless the suicide was *non compos mentis* at the time.⁴ Some sects still refuse a Christian funeral to a suicide, either by rites or burial in hallowed ground.

It is only natural that many good folk recoiled from these barbaric penalties and sought means to avoid them. For many decades in England one could seldom find a coroner's jury returning a suicide verdict without tacking on the excupatory phrase, "while suffering from a temporary mental

³ Bunzel, Bessie: Suicide, article in *Encyclopedia of Social Sciences*, 1934, vol. 14, pp. 454-459 with selective bibliography of authoritative books on suicide and its problems. A more comprehensive treatment of the subject with a longer bibliography may be found in Dublin, L. I., and Bunzel, Bessie: *To Be or Not to Be*, N. Y., Harrison Smith and Robert Haas, 1933.

⁴ Bunzel, Bessie, op. cit., supra, f. n. 3; Halsbury's *Laws of England*, ed. 2, London, Butterworth & Co., 1933, vol. 9, p. 455.

aberration," for the poor unfortunate suicide who took his life while bereft of reason was not disgraced or punished.⁵ If it was certain that the man was sane when he murdered himself, the jury could always disregard the evidence and find that he *accidentally* hanged himself or fired a ball into the roof of his mouth. These convenient mechanisms of escape continue in modern favor, not only in coroners' inquests,⁶ but in civil suits where a suicide may carry with it a financial reward from an employer or an insurance company.⁷

In some states and in England it is a crime to attempt to commit suicide⁸ or to aid or abet another by pact or otherwise in so doing,⁹ and in such instances the prosecution must prove that the act was suicidal and not accidental. Quite often a murderer will attempt to conceal his crime by arranging the scene as a suicide. If the active agency of the murderer is established, he may attempt to mitigate the offense or excuse his conduct by claiming that he merely assisted the deceased to commit suicide.¹⁰ In a criminal prosecution the State may show that the accused attempted to commit suicide as a confession of guilt.

2. At Civil Law

There are not many occasions at law, other than those to be mentioned under B, C and D, *infra*, where it becomes necessary to establish whether

⁵ Blackstone, writing in the 18th century said: "The party must be of years of discretion, and in his senses, else it is no crime. But this excuse ought not to be strained to that length to which our coroners' juries are apt to carry it, viz.: that the very act of suicide is an evidence of insanity; as if every man, who acts contrary to reason, had no reason at all: for the same argument would prove every criminal *non compos*, as well as the self-murderer. The law very rationally judges that every melancholy or hypochondriac fit does not deprive a man of the capacity of discerning right from wrong; which is necessary, as was observed in a former chapter, to form a legal excuse. And therefore if a real lunatic kills himself in a lucid interval, he is a *felo-de-se* as much as another man." 4 Blackstone Comm. 189. What Blackstone thus said almost 200 years ago in England is a succinct statement of the law today in the overwhelming majority of the United States.

⁶ In England, where a sane suicide is a crime, coroners' inquests in 4,846 suicides in 1928 returned the verdict of "*felo-de-se*" (sane suicide) in only 88 cases. East, W. Norwood: Suicide from the medicolegal aspect, British Med. Jr., 1931, ii, 241.

⁷ Nor should juries bear all of the condemnation. The corruptibility and incompetence of some coroners have led to much criticism and a substantial movement toward the medical examiners system. See abstracts from several reports on coroners' laws in Herzog, p. 7 ff. Judges, too, have contributed their full share to the avoidance of a verdict of suicide. It was the legal mind and not a statistical, scientific analysis of facts and probabilities that created the presumption against suicide, endowed it with the character of evidence, instructed juries that they might consider it as such, and so used it procedurally as to shift the burden of proof to a party who should bear no such onus. Limitations of space and subject forbid our demonstration of the fallacy of this presumption which has been blindly accepted, as the law so often does, merely because other courts have previously done so. Having served a questionable purpose during a dead age, viz., the avoidance of penalties created by the stern hand of authority and destroyed by the very arm of law supposed to enforce them, this vestigial survival, the presumption against suicide, should be exposed and excised from the corpus juris.

⁸ 92 A. L. R. 1180; 13 R. C. L. 720; 60 C. J. 997. Insanity is a defense (f. n. 5, *supra*) but drunkenness is no excuse, though it is a fact to be considered in determining whether an accused intended to commit suicide. Rex v. Doody [1854], 6 Cox, C. C. 463; Rex v. Moore [1852], 3 Car. & Kir. 319.

⁹ 13 A. L. R. 1259; 60 C. J. 998.

¹⁰ Thus, if the accused hanged his wife, it would be murder; if he assisted her to hang herself, it would be manslaughter. State v. Ludwig, 70 Mo. 412 (1879). If she hanged herself, it would be suicide, a complete defense.

a suicide was committed or an attempt thereat made. Most workmen's compensation laws provide benefits for accidental injuries and death arising out of and in the course of an employment, and exclude liability for death or disability due to injuries intentionally self-inflicted.¹¹ Under almost all compensation laws an insane suicide resulting from a compensable accidental injury is an accidental death; a sane suicide is not.¹²

A hospital or asylum or other person charged with the care of the physically or mentally ill may be liable in damages for the negligent failure to prevent a suicide.¹³ Occasionally, a person sued for damages because of injuries or death alleged to have resulted from negligence will raise the defense that such damages arose from a suicide attempt.

A few states have dramshop and civil damages acts rendering one liable for damages or death caused by the negligent sale of intoxicating liquors, the use of which by the purchaser has caused death or injury to himself or another.¹⁴ It is well known that an alarming percentage of suicides are committed either directly or indirectly as a result of acute or chronic alcoholism,¹⁵ so that in civil suits for damages for violation of such statutes it may become important to determine whether a death or injury was caused by suicide or accident.

There is a conflict in authority whether one who tortiously injures another is liable for subsequent injuries or death caused by a successful or unsuccessful suicide which resulted from unendurable pain, despondency or mental aberration arising from the first injury.¹⁶ In those jurisdictions where self-destruction is a crime, a maliciously false statement that a person committed suicide may be punishable at criminal law, but does not render one civilly liable to the surviving next of kin, unless, perhaps, in such states as Missouri, where a libel, by statutory definition, includes "any malicious

¹¹ Schneider, William R.: *Workmen's Compensation Laws*, perm. ed. 1943, vol. 4, p. 4442. For illustrative cases where the issue was accident or suicide, see 143 A. L. R. 1227.

¹² 56 A. L. R. 459; 143 A. L. R. 1227; 12 N. C. C. A. (N. S.) 298. See also f. n. 16, *infra*.

¹³ 7 N. C. C. A. 82, 88; 10 N. C. C. A. 749; 36 N. C. C. A. 618; 23 A. L. R. 1277.

¹⁴ 9 N. C. C. A. (N. S.) 176, 192-200; 23 A. L. R. 1276. As to liability of a druggist for furnishing the means to commit suicide, see 11 N. C. C. A. (N. S.) 752.

¹⁵ This fact, casually noted from a reading of a considerable number of court opinions, seems to have adequate statistical support. It has been reported that out of 1000 consecutive cases of attempted suicide admitted to Brixton prison in England, the major cause or motivation in 141 was "alcoholic impulse with amnesia," in 171 was "alcoholic impulse—memory retained," and in 31 was "post-alcoholic depression," a total of over one-third of the entire group. These figures do not include instances of insanity or other mental states due in whole or in part to alcohol. Nor do they include those cases where the suicide by the use of alcohol is finally able to screw his courage to the sticking point to carry out self-destruction premeditated for other reasons. East, W. Norwood: *Medical Aspects of Crime*, 1936, chapter V, p. 141. In another study of 1000 attempted suicides, abnormal mental states were found upon admission to a hospital in 23 per cent of the cases. In more than half of these there was a diagnosis of acute or chronic alcoholism. Lendrum, F. C.: A thousand cases of attempted suicide, *Am. Jr. Psychiat.*, 1933, xiii, 479. Menninger believes that addiction to alcohol is a form of suicide. Menninger, Karl A.: *Man Against Himself*, 1938, Harcourt, Brace & Co., N. Y., chap. 3. A readable recent book with a good bibliography of assistance both to the student and casual inquirer is Haggard, H. W. and Jellinek, E. M.: *Alcohol Explored*, 1945, Doubleday-Doran & Co., N. Y.

¹⁶ 8 N. C. C. A. 1025; 23 A. L. R. 1273; 79 A. L. R. 370, and see f. n. 12, *supra*.

defamation . . . designed to blacken and vilify the memory of one who is dead, and tending to scandalize or provoke his surviving relatives and friends."¹⁷

In some jurisdictions a will or gift made in contemplation of suicide is void if it can be proved that death resulted from suicide rather than accident or some other cause.¹⁸

B

CORONERS' INQUESTS AND DEATH CERTIFICATES

One of the most important duties of every coroner and medical examiner is the determination of whether a death was caused by disease, accident, suicide or homicide. The result of that determination is usually made a part of the death certificate required by statute. The coroner's verdict or the death certificate is often incorporated in proofs required by insurance companies. Under many statutes, the attending physician is required to make out the death certificate even though there is an inquest or autopsy. Most statutes relating to death certificates require the signer to certify whether the death was "probably" due to accident, suicide or homicide. Insurance companies usually ask the attending physician to sign one of the proofs. These certificates and proofs, prepared by coroners and attending physicians, are in many jurisdictions admitted in evidence as prima facie proof of the cause of death, rebutting the presumption against suicide, and binding and conclusive unless contradicted or explained.¹⁹

C

LIFE INSURANCE

Suicide as a Theory of Recovery. If an insured disappears and remains unheard from, his whereabouts unknown, under circumstances which do not indicate that he has died, the beneficiary must wait seven years before his insurance may be collected, for it is not until that time that a rebuttable presumption arises that the insured is dead. Therefore, it is to the interest

¹⁷ R. S. Mo. 1939, sec. 4758. Compare: *Hughes v. New England Newspaper Pub. Co.*, 312 Mass. 178, 43 N. E. (2d) 657 (1942), and annotation in 146 A. L. R. 739, "Civil Liability for Defamation of the Dead." In a recent case dealing with privileged communications to a physician, the court said: "Unless the circumstances leading to suicide are in themselves immoral or disgraceful, the mere act of self-destruction, of itself, does not necessarily tend to disgrace the memory of the decedent." *Bolts v. Union Central Life Ins. Co.* (City Ct.) 20 N. Y. S. (2d) 675 (1940).

¹⁸ 35 Yale Law J. 379; 30 Mich. Law R. 626; 32 Col. Law R. 710.

¹⁹ 93 A. L. R. 1342 (conclusiveness of proofs); Cooley, vol. 6, pp. 5466-5468, 5477-5478; Couch, vol. 8, sec. 2200 p. 7111 ff., secs. 2225-2229, p. 7213 ff. As to whether the presumption against suicide is overcome by a death certificate, coroner's verdict or similar documentary evidence, see 159 A. L. R. 171. For admissibility of death certificates and all of the statements therein contained, see f. n. 72, *infra*. In one case a sheriff summoned a local doctor to view a drowned body unknown to either of them. "I guess it is another suicide," said the doctor and so signed the death certificate. The insurance company disclaimed liability and the widow was forced to file suit. "At trial both the sheriff and the doctor abjectly confessed themselves in error for the casual way they did their business." *Eastern Commercial Trav. Acc. Assoc. v. Sanders* (C. C. A. 1, Mass.) 108 F. (2d) 643 (1940).

of the beneficiary to show that the insured disappeared under circumstances pointing to accidental death, suicide or homicide while the policy was in force. Such circumstances may be sufficient to raise an inference of death in less than seven years, or may reinforce the claim at the end of the presumptive period of seven years.

*Suicide as a Defense.*²⁰ In the absence of a statute or policy provision, suicide while sane in some jurisdictions is a defense to a life policy payable to the insured's estate, but is not a defense if the policy is payable to a third person as beneficiary, unless, however, the policy was fraudulently procured with the intention to commit suicide and thus create an estate for the beneficiary.

Unless excluded by the policy, a suicide while insane is never a defense to a life policy.

Therefore, many life policies expressly exclude liability for death by suicide. This clause will avoid payment for sane suicides, but not insane suicides, unless the exclusion reads "suicide, sane or insane," and even then a few states will allow a recovery where the insured was so insane that he did not understand the physical consequences of his act and did not intend to end his life.²¹

Although most life policies do contain the "suicide, sane or insane" exclusion, they usually have so-called incontestable clauses providing that the defense of suicide may not be raised after a certain period, usually one or two years after the policy was issued.

D

ACCIDENTAL DEATH AND DISABILITY BENEFITS

*Accident Insurance and Double Indemnity.*²² As mentioned above, an insane suicide and an unprovoked homicide are accidents, whereas sane suicide and provoked homicides, where the insured is the aggressor, are not accidents. Therefore, if a policy in its insuring clauses covers accidental deaths, the insurer is liable for an insane suicide or an unprovoked homicide, but not for a sane suicide.

Most accident policies with death benefits and most life policies with double indemnity provisions expressly re-define the coverage by excluding suicide, but this will not eliminate insane suicides unless the clause, as it usually does, reads "suicide, sane or insane." Many such policies also exclude liability for a death from injuries intentionally inflicted by another person.

²⁰ The general rules laid down in this and the next section of this paper dealing with accident insurance are so well-established that a general citation to several authoritative sources will suffice for our purposes. However, many exceptions and conflicts will be found. See: Appleman, vol. 1, chapter 19, pp. 419-451; Cooley, vol. 6, pp. 5363-5376, 5397-5489; Couch, vol. 5, pp. 4020-4022, vol. 6, pp. 4611-4667; Joyce, vol. 4, chapter LXXI, pp. 4407-4480; 37 C. J. 551-556; 29 Am. Jur. 697-704.

²¹ 153 A. L. R. 801; 138 A. L. R. 827; 35 A. L. R. 165.

²² See f. n. 20, supra, and, in addition 1 C. J. 443-444 and Cornelius, pp. 52-62.

In Missouri, a statute invalidates the policy exclusion of insane suicides, but by judicial construction does not affect the rule that a sane suicide is not an accident.²³

It is not unusual to find policies covering accidental deaths bearing other exclusions collaterally affecting death by suicide and avoiding the problem of distinguishing between accident, suicide (sane or insane), homicide, and, in some cases, disease.²⁴ Thus, a policy may, by exclusion, eliminate coverage for certain kinds of deaths whether due to accident, disease, homicide or suicide. The policy may exclude deaths due "directly or indirectly, in whole or in part," to disease, bodily or mental infirmity, infections (of certain types), medical treatment, pregnancy, hernia, freezing, sunstroke, drowning, gas, poison, gun-shot wounds, the influence of narcotics or liquor, war, aviation, violation of law, voluntary exposure to unnecessary danger, etc.

Disability Benefits. If an insured unsuccessfully attempts to commit suicide and suffers a loss of a member or disability for which, if accidental or due to disease, he would be entitled to benefits under an insurance policy, he is not entitled to such benefits even in absence of an exclusion in the contract, unless he was insane at the time of the attempt.²⁵ In these cases, as in all of those heretofore mentioned, it will be necessary to determine whether the act was accidental or suicidal.

III

PROCEDURAL LAW—HOW THE ISSUE IS DECIDED ²⁶

A

PLEADING, BURDEN OF PROOF AND PRESUMPTIONS ²⁷

As a general rule it is the duty of the party who asserts a fact necessary to his cause of action or affirmative defense to plead and prove it. Therefore, in a suit on a *life* insurance policy where suicide is an affirmative de-

²³ The Missouri statute barring suicide as a defense was for many years misconstrued to make a sane suicide an accident! Missouri became a mecca for suicides. For a while there was a veritable flurry of suicides on street cars and railroad trains, since a sane suicide not only permitted the beneficiary to collect double indemnity, but, under some policies covering accidents on public conveyances, triple indemnity as well!

²⁴ Such exclusions are fully discussed in Appleman, vol. 1, chapters 22-32; Cooley, vol. 6, pp. 5293-5397; Couch, vol. 6, chapter 17; Joyce, vol. 4, chapter LXX.

²⁵ There may be some conflict on the question. *Elwood v. New England Mut. Life Ins. Co.*, 305 Pa. 505, 158 Atl. 257 (1931); compare *Prudential Ins. Co. v. Rice*, 222 Ind. 231, 52 N. E. (2d) 624 (1944). See 49 U. of Pa. Law R. 1365.

²⁶ Here will be found some of the reasons so many apparently unjust jury verdicts have been permitted to stand. Here is drawn the heavy line separating the province of the court from that of the jury. Until the judicial process is understood it cannot be criticized or even materially assisted by the investigator. The layman or physician should not be too quick to find fault with these rules, for they are the very basis of the jury system, and for the most part and with very few exceptions have had the support of jurists for years in all states.

²⁷ "Perhaps no topic of the law has perplexed the courts more than the scope and effect of legal presumptions. The complexities and subtleties of the subject, enhanced no doubt by the variant theories regarding them and the confusion of thought manifested in the discussion of the questions incident to them, have given rise to a condition that has been characterized as a 'welter of loose language and discordant decisions.'" *Tyrrell v. Prudential Ins. Co.*, 109 Vt. 6, 192 Atl. 184 (1937).

fense, the burden of proof is on the defendant to plead and prove that the insured committed suicide. On the other hand, in a suit on an *accident* insurance policy or on a life policy for *double indemnity*, the defendant is not required to plead or prove suicide as a defense since the plaintiff has the burden of pleading and proving that death resulted from a cause within the coverage, accident, so that the defendant by merely denying the plaintiff's assertion may prove any fact, such as suicide, which tends to disprove the plaintiff's theory of accident. The failure to distinguish a suit on a life policy from one for accidental death benefits (double indemnity or accident policy) has introduced much conflict, misunderstanding, confusion and injustice into the trial and decision of *accident* insurance cases.²⁸

The phrase "burden of proof" means "the risk of non-persuasion" or the duty of affirmatively proving one's case or defense, so that if there is no substantial evidence in support thereof, the issue cannot be submitted to the jury, but must be ruled out of the case as a matter of law by the judge. If there is substantial evidence warranting the submission of the issue to the jury, then the party carrying the burden of proof must establish his case to the satisfaction of the jury by a preponderance or greater weight of the credible evidence.

The burden of proof never shifts, but continues to abide throughout the trial with the party upon whom it was originally cast. However, the burden of going forward with the evidence does shift, so that after one litigant has made out a *prima facie* case and thus, for the time, sustained his burden of proof, the duty of going forward with evidence to meet the *prima facie* case shifts to his adversary.

These rules are of considerable importance because it is almost universally accepted that as soon as there is proof that a death was violently met, the law presumes that the death was not caused by suicide or murder. Therefore, in a suit for accidental death benefits or for workmen's compensation, the beneficiary is said to make a *prima facie* case merely by proving that death was violent, and no further evidence is required unless that *prima facie* case is met by the defendant who has the burden of going forward with evidence (but not the burden of proof).

However, a presumption is not evidence; it is merely a rule of procedural law covering the duty of going forward with evidence. Once substantial evidence of the facts appears, whether introduced by the plaintiff or the defendant, or both, the presumption disappears from the case, has no probative

²⁸ In suits on *life* insurance policies where the evidence is entirely or mostly circumstantial, the defendant is required not only to produce substantial evidence of suicide but also to exclude every reasonable hypothesis of accident or homicide before it is entitled to a directed verdict as a matter of law. However, this rule does not apply in accident cases, since the defendant's failure to prove suicide as a matter of law does not relieve plaintiff of his burden of proving accident, so that if there is no substantial evidence of accident, or if the cause of death can only be determined by speculation, conjecture or surmise, then and in either such event the plaintiff has failed to carry his burden of proof and the defendant is entitled to a direct verdict. The insurer "is not required to eliminate every speculative, fantastic, conjectural, frivolous and imaginary hypothesis of death in any other way." *N. Y. Life Ins. Co. v. Hunter*, 60 Ariz. 416, 138 P. (2d) 414 (1943).

force, has no weight as evidence, and the jury cannot be instructed to consider it in arriving at a verdict.²⁹

There are several other presumptions which the law occasionally recognizes and which may have some bearing on the decision of cases within the subject under consideration. There is a presumption that all men are sane and conscious of the consequences of their actions. Therefore, when the insured has committed suicide and plaintiff is relying upon the theory that he was insane and his death thus accidental, the burden of proving that the insured was insane at the time of the act rests upon the plaintiff.³⁰ The mere fact that the insured committed suicide raises no presumption of insanity so far as the court is concerned, although many laymen, physicians and psychiatrists think differently, much depending upon their definition of insanity.³¹ On the other hand, proof that the insured was insane at the time of an unexplained violent death may destroy the presumption against suicide.³² We again sound the warning note that all of these presumptions are not evidence though they may, temporarily and until rebutted, take the place of evidence.

B

ADMISSIBILITY OF EVIDENCE

Evidence is admissible in a trial if it is material, competent, relevant, and satisfies prescribed modes of proof. It is material and relevant if it tends to establish the truth of the fact sought to be proved, i.e., if it might be accepted by reasonable men as tending to prove the fact. The present tendency is to relax the rules of evidence and admit much evidence which was formerly withheld from a jury.

It is, of course, entirely proper to prove all of the facts and circumstances leading up to, surrounding and following the injury which tend to establish

²⁹ The sardonic comment of Judge Belt in *Wyckoff v. Mutual Life Ins. Co. of N. Y.*, 173 Ore. 592, 147 P. (2d) 227 (1944), though unjustified, requires citation: "Some text writers, law professors and judges who have espoused the Wigmore doctrine have vied with one another in an effort to show how flimsy and unsubstantial a presumption of law really is. This 'phantom of the law' has been likened to 'bats flitting about in the twilight and then disappearing in the sunshine of actual facts,' and to a house of cards that topples over when rebutted by evidence. It remained for Professor Bohlen to head the class when he said a presumption of law was like Maeterlinck's bee which, after functioning, disappeared."

³⁰ *Laventhal v. N. Y. Life Ins. Co.* (D. C., Mo.) 40 F. Supp. 157 (1941) a case decided solely upon presumptions. It must be shown that the insured was insane at the time of the act, so that plaintiff may encounter some difficulty where the insured is subject to only temporary fits of insanity. Appelman, vol. 1, p. 436. Blackstone long ago recognized the fact and burden of proof, f. n. 5, *supra*.

³¹ 37 C. J. 620; *N. Y. Life Ins. Co. v. King* (C. C. A. 8, Mo.) 93 F. (2d) 347 (1937). As to disqualifying jurors who believe so, see *Edwards v. Business Men's Assur. Co.*, 350 Mo. 666, 168 S. W. (2d) 82 (1942). However, it has been held that suicide is evidence of insanity. *Horvath v. N. Y. Life Ins. Co.*, 65 S. D. 480, 275 N. W. 258 (1937); *Wigmore on Evidence*, ed. 2, secs. 228, 2500, 2501. Despite this rule, it is also held that suicide does not overthrow the presumption of sanity.

³² *Cooley*, vol. 6, pp. 5454-5459. "The presumption [against suicide] in the case of a sane man is based upon his sanity, and the fact of insanity being shown, the ground of the presumption is gone." *Horvath v. N. Y. Life Ins. Co.*, 65 S. D. 480, 275 N. W. 258 (1937) and cases cited. The better rule is that insanity merely destroys the presumption against suicide and does not create any new presumption in favor of it. 112 A. L. R. 1278.

its cause and the motive or lack of motive for suicide at the time of its infliction. The courts are also very liberal in permitting proof of any fact which might prove or disprove the presence or absence of a motive for suicide.

There is almost no limit to the type of evidence developed by the ingenuity of litigants to prove or disprove theories of the cause of death. The best rules to guide the investigator are: (1) assume that the evidence is admissible; (2) gather, fix, and preserve it in such form that it will be available, useful, and not subject to contradiction months or years later when it may be needed; (3) obtain all of the evidence possible of a corroborative nature with special emphasis on the use of methods not subject to impeachment, i.e., the use of disinterested witnesses, signed statements, photographs, and scientific proof³³; (4) do not neglect negative evidence such as written, signed statements that witnesses in a position to know a fact did not know it, because it is a continual source of chagrin to the lawyer to find witnesses, who orally stated to the investigator that they did not know a fact, present in court months later with vivid recollections of the most minute details.

C

SUFFICIENCY OF THE EVIDENCE

Although the jury is the sole judge of the credibility of the witnesses and the weight to be given to their testimony, it is the special province and duty of the court to determine, as a matter of law, whether there is sufficient substantial evidence in support of an issue from which a jury could find the facts in favor of the party with the burden of proof. In deciding this question of law, the court is obliged to view the evidence in that light most favorable to the party carrying the burden of proof, giving to him the benefit of all logical inferences which may be drawn from all of the evidence and rejecting all evidence opposed thereto, except that evidence of his adversary consistent with the proponent's testimony and not in conflict with his theory of recovery. After so considering the evidence, the issue is one for the jury and cannot be ruled by the court as a matter of law if the minds of reasonable men might differ as to the ultimate fact in issue. If the evidence is documentary

³³ A good illustration is *Gilpin v. Aetna Life Ins. Co.*, 234 Mo. A. 566, 132 S. W. (2d) 686 (1939) where the deceased with adequate motive for suicide (syphilis, debts, involvement with another woman, etc.—all disputed) was found in his car with a revolver wound in his head under circumstances which the court held might indicate that death was either accidental or suicidal. Among other conflicts in the evidence were the existence, extent and location of powder marks, the distance the revolver must have been from the head when the shot was fired, the presence or absence of a bruise on the hand and, of all things, the location of the entrance wound itself. The coroner, a pathologist, said that it was above the right ear and that the path of the bullet was straight through the head. The court felt helpless to accept this evidence of a scientific, disinterested witness as conclusive, and said that it was for the jury to say whether such evidence should be rejected in favor of that given by friends of the deceased (and the beneficiary) who variously located the entrance wound in the middle of the forehead, over the right eye, and at the temple! A photograph would have avoided such conflicts resulting either from incompetence or dishonesty on the one side or the other. Photographs of corpses are admissible in evidence. 159 A. L. R. 1413.

or uncontested or the facts are agreed to, then the court may decide the issue in favor of the plaintiff as a matter of law. The court may be convinced that the preponderance or weight of the evidence is in favor of one party, but, except in a few states, it may not determine the case on its view of the weight of the evidence so long as there is sufficient substantial evidence to the contrary. In such case, the jury alone is privileged to decide the issue.

Thus, if the widow-beneficiary testifies that her husband was happy and had no domestic or financial troubles, it is the privilege of the jury to believe her and reject the positive contrary testimony of ten witnesses who testify for the insurance company. The coroner's physician may testify to the location of wounds and presence or absence of powder burns, but an interested relative of the deceased may testify and be believed to the contrary. When photographs and documentary evidence are introduced, suicide notes, for instance, the court and jury both are usually inclined to accept such evidence as establishing the facts, unless they are explained or in some way weakened or impaired.

These observations indicate how important it is to "clinch" a fact beyond any dispute at the time of the original investigation. Let no one *suppose* that *his* word will be accepted over that of any other man when both stand before a jury. And let there be no one so naive as to believe that witnesses are never mistaken or dishonest. There are often strong motives and virtually no real deterrents to perjury, and even where testimony is not knowingly false, the witness may be mistaken and do equal damage. There is no fact immune from rebuttal by dishonesty, ignorance or both. Caveat investigator!

In recent years most courts have become more impartial in the administration of insurance law. More stress is laid on common sense and sound scientific testimony than on artificial presumptions and rules of law. With an understanding of the burden of proof and effect of presumptions there is an increasing tendency to return to three fundamental principles applied in all other cases: *first*, evidence must be substantial before a jury is allowed to accept it as proof of the ultimate fact; *second*, speculative possibilities are not evidence and the jury should not be permitted to find a verdict by mere speculation and conjecture³⁴; and, *third*, where under the evidence an injury

³⁴ A "fanciful theory of accident" cannot be spun out on bare possibilities since verdicts must rest upon probabilities. *Love v. N. Y. Life Ins. Co.* (C. C. A. 5, Miss.) 64 F. (2d) 829 (1933). "We do not think these theories can be accepted with any show of reason, or that they would be seriously considered if this were not a controversy between a bereaved widow and an insurance company." *Brotherhood of Maintenance of Way Employees v. Page*, 197 Ark. 498, 123 S. W. (2d) 536 (1939). "Jurors are not permitted to shut their eyes to what everybody else sees and understands and wander off into fields of imagination and suspicion in order to reach verdicts. Courts are more and more realizing and declaring that they must not permit themselves to be more ignorant than anybody else or fail to see what is plain to everyone and everybody except a court." *Deweese v. Sovereign Camp, W. O. W.*, 110 Kan. 434, 204 Pac. 526 (1922). This result is, as indicated, largely chargeable to erroneous concepts of the burden of proof and the presumption against suicide, so that too frequently "judge and jury alike have been unable to take a common sense view of the facts of life, and have seemed to be the only persons in the community who did not clearly understand what had taken place." *Jefferson Standard Life Ins. Co. v. Clemmer* (C. C. A. 4, Va.) 79 F. (2d) 724 (1935).

or death might or could have resulted from either one of two causes for only one of which the defendant would be liable, and the plaintiff has not sustained his burden of proving that such cause was the more probable, then no recovery may be had.³⁵

IV

EXPERT AND NON-EXPERT EVIDENCE OF PROBATIVE FORCE

Suicide is death from (1) injuries self-inflicted (2) with intention to end one's life. Accidental injuries may or may not be self-inflicted; they are usually caused by some accidental means external to the individual; they are, of course, never inflicted with intention to end one's life. Therefore, in seeking evidence of probative force to distinguish between accident and suicide, we naturally turn to two sources: (A) External Evidence, to determine whether the injury was self-inflicted, and (B) Internal Evidence, to determine if there was an intention to end one's life. This evidence may be direct or circumstantial. According to Blackstone, "evidence signifies that which demonstrates, makes clear, or ascertains the truth of the very fact or point in issue, either on the one side or the other."³⁶ "Direct or positive evidence is to the precise point in issue, as in the case of a homicide, that the witness saw the accused inflict the blow."³⁷ In a suicide case the testimony of an eye-witness, a suicide note or other declaration of intent, and an unquestioned photograph may be termed direct evidence, and this is important because in such cases there is no need to resort to circumstantial evidence or lay stress on motive.³⁸ "Circumstantial evidence is that which relates to a series of other facts than the fact in issue, which by experience have been found so associated with that fact that in the relation of cause and effect they lead to a satisfactory conclusion."³⁹ The distinction is of some importance because of the frequent insistence that where evidence is circumstantial it must negate every reasonable hypothesis of death by accident.⁴⁰ This, as we

³⁵ "Where proved facts give equal support to each of two inconsistent inferences neither is established, and judgment must go against the party on whom rests the necessity of sustaining one of them against the other." *N. Y. Life Ins. Co. v. Ittner*, 64 Ga. A. 806, 14 S. E. (2d) 203 (1941), dissent by Felton, J., citing cases; *N. Y. Life Ins. Co. v. Prejean* (C. C. A. 5, La.) 149 F. (2d) 114 (1945). "There were no facts or circumstances from which the jury could infer legitimately to the exclusion of other inferences equally plausible that the insured's death resulted from accident." *Waldron v. Met. Life Ins. Co.*, 347 Pa. 257, 31 A. (2d) 902 (1943). "In such circumstances, under contradicted evidence, the party having the burden of proof cannot prevail." *Christensen v. New Eng. Mut. Life Ins. Co.*, 71 Ga. A. 393, 31 S. E. (2d) 214 (1944), s. c. 197 Ga. 807, 30 S. E. (2d) 471, s. c. (unreported Ga. A.) 9 CCH Life Cases 268. Of course, if there is no substantial evidence of accident, then the issue of accident cannot be submitted to the jury and it is immaterial where the burden of proof lies in a suit for accidental death benefits. *Fox v. Mut. Ben. H. & A. Assoc.*, 61 Ga. A. 835, 7 S. E. (2d) 403 (1940).

³⁶ 3 Blackstone Comm. 367.

³⁷ Jones, vol. 1, p. 16.

³⁸ *Webster v. N. Y. Life Ins. Co.*, 160 La. 854, 107 So. 599 (1926), a learned opinion frequently cited and followed.

³⁹ Jones, vol. 1, p. 16.

⁴⁰ *Cooley*, vol. 6, p. 5473; *Gilpin v. Aetna Life Ins. Co.*, 234 Mo. A. 566, 132 S. W. (2d) 686 (1939); *N. Y. Life Ins. Co. v. Satcher*, 152 Fla. 411, 12 So. (2d) 108 (1943).

have demonstrated, may be true in criminal cases, but it is not true in civil cases.⁴¹

Once all of these rules of law are understood, we are ready to discuss evidential problems in distinguishing accident from suicide. "But that is a question of fact, because, like the question of what is the proximate cause of an injury, it is not a question of science or legal knowledge, but each case must necessarily stand on its own probative facts and circumstances," and no one case can serve as a complete precedent and be decisive of any other.⁴²

A

EXTERNAL EVIDENCE: WAS THE INJURY SELF-INFLICTED?

First, determine the physical cause of death.

Was it due to natural or unnatural causes: disease, poison, gun-shot wound, gas, drowning, a fall or impact? Where there are multiple wounds as possible causes of death, one must decide which injury was inflicted first, whether it alone was sufficient to cause death, whether the other injuries could have been accidentally or self-inflicted thereafter, and what diseases and wounds and other causes actually contributed to bring about death. Burning may be used to conceal a suicide or homicide. A determination of the concentration of alcohol in the blood may help to prove that the burning resulted from an alcoholic stupor.⁴³ A cerebral hemorrhage or coronary occlusion may precede and cause a fall or auto accident, which in turn may cause death,⁴⁴ or death may result from the hemorrhage or clot despite extensive injuries suffered in the fall. If a body is recovered from water it must be determined, if possible, whether death resulted from drowning or whether it preceded immersion and was caused by disease, suicide or homicide.⁴⁵ Carbon monoxide determinations should readily disclose whether death occurred as a result of inhalation of that gas where the body was found

⁴¹ *Cox v. Met. Life Ins. Co.*, 139 Me. 167, 28 A. (2d) 143 (1943). See also: *Mut. Life Ins. Co. of N. Y. v. Hamilton* (C. C. A. 5, Fla.), 143 F. (2d) 726 (1944).

⁴² *Webster v. N. Y. Life Ins. Co.*, 160 La. 854, 107 So. 599 (1926). The court did not mean to say that scientific knowledge and proof would not be evidence. It meant that "the entire question is one of fact, and not one of law." *Soecker v. Met. Life Ins. Co.*, 51 Cal. A. (2d) 479, 125 P. (2d) 105 (1942). See also *infra*, n. 74.

⁴³ Jetter, Walter W.: When is death caused or contributed to by acute alcoholism?, *Clinics*, 1943, i, 1487. The presence or absence of alcohol in the blood in a sufficiently high concentration may make accident plausible or "may account for suicidal dementia or for behavior changes likely to provoke assault." Moritz, Alan R. and Lund, Herbert: Special evidentiary objectives of the medicolegal autopsy, Jr. *Tech. Meth. and Bull. Internat. Assoc. Med. Mus.*, 1943, No. xxiii, p. 71. The blood alcohol determination may assist the beneficiary in showing that the death was accidental; or in any case of death by burning or other cause, the insurer may wish to establish the fact in order to invoke provisions of the policy excluding liability if death occurred while the insured was intoxicated or under the influence of liquor. It is usually not necessary to show that there was a causal connection between the condition and the death. Appleman, vol. 1, sec. 465-582. As to admissibility and weight of evidence based on scientific tests for intoxication or the presence of alcohol in the system, see 127 A. L. R. 1513; 159 A. L. R. 209; 29 Va. L. Rev. 749 (1943).

⁴⁴ Such a death is usually held to have been effected by accidental means, but there is no liability in most states if the policy further provides that it will not cover a loss resulting from or caused directly or indirectly or in whole or in part by disease. Cornelius, pp. 42-50.

⁴⁵ *Kahn v. Met. Life Ins. Co.* (Mo. Sup.) 240 S. W. 793 (1922), where there was evidence that the death might have been caused by a heart attack, either alone or causing a fall from a boat, or by poison or by drowning or a combination of those causes.

in a garage, a gas-filled room or burning building.⁴⁶ Since almost all hangings are suicidal and not accidental or homicidal, one should be certain that the body was not strung up after a homicidal death to conceal the crime. Deaths from poison are the most difficult properly to prove in a court of law. There are few toxicologists who can fully qualify in that field. The usual hospital or coroner's autopsy generally obtains nothing more than the barest presumptive evidence of death from poisoning. A carefully conducted cross-examination can in almost every case destroy or seriously impair an opinion that death resulted from poisoning.

Second, note the location, size, direction or course, nature and extent of all wounds or other evidence of the body's reaction to the lethal agency. This would also include any evidence on the body, clothing or surroundings furnishing any clue to the nature of the weapon or agency causing death and its position before, at the time, and after it acted upon the deceased. Specific evidence in various types of violent deaths will be dealt with in division V of this paper.

Medical jurists have evolved many *general* rules, most of them of little practical value, for distinguishing accidental from suicidal or homicidal wounds and deaths. All of such general rules about the "usual" case have not one but many exceptions, and no one bit of evidence should alone decide the issue. Moreover, some of these rules or "clues" have more value than others in one case, but their *relative* importance may change in another case.

Illustrative of the numerous physical circumstances stressed by courts, which may furnish external evidence of assistance to the jury are: the time, place and circumstances of the death, the nature of the death wound, the opportunity which deceased had to kill himself at other times, the position of the body, the location of a bullet or other wound, the course and depth of the wound, the presence or absence of powder marks or singeing, the relative location of the instrument employed to take life, the presence or absence of evidence of violence or an out-cry, etc.⁴⁷

Third, determine the source of the lethal agency, if any, which caused the death, the deceased's access to it at the time when the injury was presumably inflicted, and, finally, the physical relation of the agency to the deceased.

Fourth, reconstruct the events taking place when the injury occurred.

This is exactly what the jury will be thinking of from the opening moments of a trial. Is there substantial circumstantial evidence from which a logical conclusion can be reached, or must the investigator speculate and

⁴⁶ Gettler, A. O. and Freimuth, H. C.: The carbon monoxide content of blood under various conditions, *Am. Jr. Clin. Path.*, 1940, x, 603; Merkel, H.: Findings of diagnostic value on burnt and charred bodies, *Deutsch. Ztschr. f. d. ges. ger. Med.*, 1931, xviii, 232 (abstracted in *Arch. Path.*, 1932, xiv, 425). Where a body is found burned or exposed to carbon monoxide and there is no significant concentration of that gas in the blood, the person died from other causes than burning or carbon monoxide poisoning before he was exposed to any significant amount of carbon monoxide. The blood within the heart or major vessels of a dead body will not absorb carbon monoxide from the air, but the peripheral parts of the body may absorb enough of the gas to give a so-called "characteristic" cherry-red coloring and thus mislead the casual viewer.

⁴⁷ 17 *Amer. & Eng. Anno. Cas.* 35-37; *Ann. Cas.* 1913 C, 1260.

guess in order to reconstruct the event? Is all of the evidence consistent with accident or suicide, or both?

B

INTERNAL EVIDENCE: WAS THE INJURY INTENTIONAL?

Wigmore has said that "the evidential data available to prove the doing of any human act fall always into three groups, viz., prospectant, concomitant and subsequent."⁴⁸ We have borrowed his classification in dealing with the issue of whether an injury was intentionally self-inflicted.

1. Prospectant Evidence

Incentives and Deterrents. The proponent of the theory of accident will invariably show that the deceased had no reason or motive to commit suicide, and that a number of circumstances combined to deter him from such an act. The opponent, urging suicide, will attempt to show that such deterrents were lost or weakened and that the deceased had every incentive to abandon life and seek death by the escape mechanism of suicide. It is just as important for the beneficiary of an accident policy to show the absence of motive and the presence of natural deterrents as it is for the insurer to prove the contrary to be true.⁴⁹ However, it is not necessary to the theory of suicide that a motive be found.⁵⁰ The springs of human action are often hidden and of such obscure origin that not even a psychiatrist with the full voluntary cooperation of his patient can find them.⁵¹ Some suicides are committed for ulterior motives never discovered,⁵² and some occur not for any deep-lying or long-existing reason, but for shallow reasons as a result of sudden impulse

⁴⁸ Wigmore, John H.: Circumstantial evidence in poisoning cases, *Clinics*, 1943, i, 1507.

⁴⁹ "Motive is important and oftentimes its existence or lack of existence turns the scales against or in favor of the theory of suicide." *Bayles v. Jefferson Standard Life Ins. Co.* (La. A.), 148 So. 465 (1933). The beneficiary will attempt to show any one or more of the following facts which have been said to indicate that the death may be accidental: youth, good health, good habits, sobriety, industriousness, religious inclinations, a merry, cheerful disposition, "slept and ate well," good spirits, happy home life, kindness and affection to children, enjoyment of friends and genial companions, freedom from debt, satisfactory employment, etc. The insurer will look for evidence to the contrary. 17 *Amer. & Eng. Anno. Cas.* 38-39.

⁵⁰ A motive helps to decide the case, but is not necessary to a finding of suicide. *N. Y. Life Ins. Co. v. Sparkman* (C. C. A. 5, Fla.), 101 F. (2d) 484 (1939). "Motive was not an essential element requiring either proof on the part of the plaintiff or disproof on the part of the defendant." *Leahy v. Travelers Ins. Co.* (D. C., Ohio), 42 F. Supp. 26 (1941).

⁵¹ "It is no reflection upon the profession of psychiatry to say that it necessarily deals in a field of conjecture. Even in the diagnosis of actual insanity, cases are rare in which trained psychiatric witnesses do not come to opposite conclusions. The opinions here relate to neurosis, a condition short of insanity, on which there are countless theories and infinite diagnostic possibilities. It is difficult to conceive of records in which the right of cross-examination is more important than the conjectures of a psychiatrist on a psychoneurotic condition." *N. Y. Life Ins. Co. v. Taylor* (C. C. A., Dist. Col.), 147 F. (2d) 297 (1944), passing on the admissibility of hearsay evidence and opinions contained in hospital records.

⁵² The trial of John Thomson in 1857 for the murder of Agnes Montgomery at Eaglesham, near Glasgow, was the first case in Scotland of murder by prussic acid. The defense attempted to show that there was no motive for the deed. The Lord Justice Clerk, John Hope, instructed the jury: "It is a rash thing to attempt to set a bound to man's malignity, or to suppose that, because your honest and innocent hearts cannot enter into the motive of one committing such a crime, guilt must be excluded. We know not the depths of the depravity and malignity of the human heart, and numbers of desperate criminals would escape if one were to test things in this way, and to lay aside evidence of matters of fact from our inability to understand what led the man to do the deed." 27 *Jur. Rev.* 76 (1915).

and post-alcoholic and disease states unknown before death and undiscovered thereafter.⁵³ Then again, after a suicide, the family and friends are reluctant to reveal any facts which would reflect on them or the memory of the deceased. An opportunity to collect money from an employer or an insurer furnishes an additional reason for reticence.

The usual deterrents and incentives to suicide may be found by reference to age, domestic relations, financial circumstances, lack of employment, fear of arrest or imprisonment because of embezzlement or any other crime, physical and mental health (including acute and chronic alcoholism and post-alcoholic and disease states), frustrated love, religion, superstitions, philosophy and attitude toward life and death, etc.⁵⁴

Knowledge of the Lethal Agency. It should be determined whether or not the deceased knew that the deadly agency which caused his death was capable of that effect. There could be no intention to end life unless the deceased knew the existence, presence or imminence of the thing which took his life and its deadly character. Acts preparatory to the deed may disclose the knowledge and intention requisite to proof of suicide, or the absence of such knowledge.⁵⁵

Previous Attempts. Great stress is and should be laid upon the discovery that the deceased had previously attempted to commit suicide. Such attempts may have been made at other times or at the time of the successful act. Illustrative of the latter and indicative of suicide are the "hesitation" cuts in suicide by cutting, a "snapped" but unfired cartridge ahead of the exploded one, multiple wounds in several methods of suicide (cutting, shooting, etc.), the use of several poisons or a dose many times both the medicinal and lethal dose, etc. So also the suicide may resort to several different methods at the same time.

⁵³ "His allegedly cheerful spirits up to the time he was seen upon the bridge does not necessarily outweigh the evidence of suicide. It is a matter almost of common knowledge that many who commit suicide do not give any indication beforehand of their self-destructive intent. In many cases suicide results from a sudden impulse. What motivates persons to commit suicide is often a mystery." *Waldron v. Met. Life Ins. Co.*, 347 Pa. 257, 31 A. (2d) 902 (1943). "The physician should not be misled by the previous normal behavior of the individual or the statement by relatives that the deceased was not the person to do such a thing, and that they are quite satisfied that he would never make such an attempt on his life. The most unlikely people sometimes take their own lives and their behavior immediately before the act frequently gives no indication of their intentions. . . . A suicide may be the last person suspected of taking his own life and may do the most surprising things to achieve this end." Kerr, p. 88 et seq.

⁵⁴ After a study of 1000 consecutive cases of attempted suicide admitted to Brixton prison in England, Dr. W. Norwood East found that the major causes and motives were: Alcoholic impulse with amnesia (141), alcoholic impulse—memory retained (171), post-alcoholic depression (31), out of work (112), business worries (27), destitution (64), domestic troubles (120), fear of imprisonment or of arrest (41), depression from various causes (20), morbid mental states (18), weak-mindedness (46), neurasthenia (8), epilepsy (10), insanity (123), ulterior purposes (61), other causes, such as shame, mistake under alcohol, etc. (7). See f. n. 15, supra. From our study of cases coming before coroners and courts for decision, there is seldom a single cause or motive for suicide. Usually there is an accumulation of motives culminating in an act of suicide either on impulse or for some slight additional reason which the average, normal man could overcome.

⁵⁵ "Preparation for an act is evidence of intent to carry it out. . . . The gun was assembled, loaded, and discharged. No occasion for assembling it existed other than the use to which it was put." *Justice Fairchild, dissenting in Tully v. Prud. Ins. Co.*, 234 Wis. 549, 291 N. W. 804 (1940).

Written or Oral Declarations of the Deceased. Many suicides leave notes removing all doubt concerning the intentional character of the act. Where such a note is discovered, the court should declare as a matter of law that the act was suicidal no matter how accidental the act may seem, unless, of course, the note was ambiguous or was written at some previous time in connection with a contemplated suicide never executed. It may be shown, also, that at some time, not too remote from the time of death, the insured threatened to commit suicide or hinted that he would do so, was tired of life, was going to end it all, would be better off dead, etc.⁵⁶ The opposite party is entitled to draw attention to the absence of notes and threats, and the oral and written declarations of the deceased indicating that a short time before his death he made specific plans for the future beyond the time of his death.

2. Concomitant Evidence

Physical and Mental States. The likelihood or unlikelihood that the act was intentional may turn upon whether the deceased's mind was clear enough to form the intention, or was so befogged as to make the intention that much easier to execute, or was so befuddled and confused as either to prevent the formation of the intention or increase the probability of an accidental death.⁵⁷

⁵⁶ Declarations a long time before the act are inadmissible. Cooley, vol. 6, p. 5469. Statements made to a lawyer are admissible if not privileged. *Modern Woodmen of America v. Watkins* (C. C. A. 5, Fla.), 132 F. (2d) 352 (1942). As for admissibility of statements made to a physician or in hospital records, the rule will vary from state to state, depending upon statutes relating to privilege, the keeping of hospital records and a determination of what is and what is not hearsay. See Couch, vol. 8, sec. 2201; 75 A. L. R. 378; 120 A. L. R. 1124; *N. Y. Life Ins. Co. v. Taylor* (C. C. A., Dist. Col.), 147 F. (2d) 297 (1945), and cases cited. Compare *Buckminster's Estate v. Comm. Int. Rev.* (C. C. A. 2, Tax Court), 147 F. (2d) 331 (1944), disagreeing with the Taylor opinion in its interpretation of the Federal Shop Book Rule, 28 U. S. C. A., Sec. 695, as it applies to hospital records. These appellate courts, it seems, could not agree upon what the United States Supreme Court had ruled in construing the same statute! *Palmer v. Hoffman*, 318 U. S. 109, 63 S. Ct. 477, 87 L. Ed. 645, 144 A. L. R. 719. In *Bolts v. Union Central Life Ins. Co.* (City Ct.), 20 N. Y. S. (2d) 675 (1940), the court held that the deceased's statement to a doctor that she did not care to live was not privileged since the doctor already knew that she had attempted her life and the statement was unnecessary to the treatment. The court laid down the generally recognized rule that a physician is barred from testifying to any fact elicited which is necessary to his diagnosis or treatment or may tend to disgrace the memory of the patient or is confidential.

⁵⁷ Although most policies contain a clause excluding death from suicide, sane or insane, it has been held in some states that since suicide involves an intentional act, the insured must have had the mind and mentality enough to know that he was taking his own life. 153 A. L. R. 801. A self-inflicted injury may be accidental when received in a delirium or during intoxication or while in some other mental condition where suicide was not intended. Therefore, it is important to determine the deceased's state of mind when the act was committed. Appleman, vol. 1, p. 438, and examples there cited. The use of drugs may so confuse the mind as to preclude any intention of suicide and even cause accidents. *Feldmann v. Connecticut Mutual Life Ins. Co.* (C. C. A. 8, Mo.), 142 F. (2d) 628 (1944). Compare *Aubuchon v. Met. Life Ins. Co.* (C. C. A. 8, Mo.), 142 F. (2d) 20 (1944); see also majority and dissenting opinions in *Lincoln Petroleum Co. v. N. Y. Life Ins. Co.* (C. C. A. 7, Ill.), 115 F. (2d) 73 (1940). In that case the deceased, while intoxicated, quarrelled with his wife, who, to scare him climbed onto the sill of a fourth floor hotel window, then slipped and fell, slumped in a heap but unhurt. He must have thought she was dead, for he edged himself across the sill (which was 3 feet high and in back of a radiator) and then, ignoring warning cries, plunged down head-first with a shout of "Down I come." A jury found in favor of his widow—an accidental death. One judge on appeal thought that the death would be accidental if his death resulted "from an unreasonable or foolish act committed while under the influence of intoxicating liquor or while suffering from great mental or emotional shock." The other two judges reversed the judgment holding: "Whether his mind was cleared by

Was the deceased confused, drugged, intoxicated, insane or in a somnambulist, "automatic," compulsive, impulsive or delirious state? The same answer may be used to argue both for and against accident! So, also, it may be found that the deceased, at the time of his death, had other physical disabilities or abilities which give a clue to what took place when he died.⁵⁸ He may have been epileptic or otherwise afflicted with diseases causing syncope, convulsive or psychomotor actions.⁵⁹ He may have been in a physical state such that a medicinal dose of a poison taken without suicidal intention resulted directly or indirectly in death.⁶⁰ He may have had a physical illness producing delirium.⁶¹

the shocking and sobering spectacle he had just witnessed or whether his drunken condition still clogged his mental faculties is immaterial for the exception to insurance liability in each policy covered 'self destruction,' 'whether sane or insane.' Avoidance of this exception is not shown either by the action of one mentally perplexed to the point of insanity or by the less disturbed but nevertheless highly confused mental state of one who is badly intoxicated. A fair construction of this exception clause necessitates a reasonable application to facts. Courts are not justified in holding that it applies to self-destruction by one who is insane, but does not cover self-destruction by one who is drunk, but whose drunken mental state does not reach the point of alcoholic insanity." The ramifications of this question are enormous, but lead us into theories of accidental means and beyond the scope of this paper.

⁵⁸ Eye removed at hospital explaining fall from hospital window. *Smith v. Durham Life Ins. Co.*, 202 S. C. 392, 25 S. E. (2d) 247 (1943). Subject to "fainting spells" (not enough, though other evidence of accident was present). *Brotherhood of Maintenance of Way Employees v. Page*, 197 Ark. 498, 123 S. W. (2d) 536 (1939). Physical impairment of hand accounting for unintended discharge or abnormal manner of handling gun. *K. C. Life Ins. Co. v. Bowman* (C. C. A. 9, Idaho), 102 F. (2d) 510 (1939); *Union Central Life Ins. Co. v. Cooper* (C. C. A. 5, Ala.), 115 F. (2d) 222 (1940). Under opiates and ill in bed, death from burning. *Brooks v. Met. Life Ins. Co.* (Cal. Sup. Ct. in banc) 163 P. (2d) 689 (1945), disagreeing with opposite conclusion of the California Court of Appeals (Cal. A.), 159 P. (2d) 424 (1945). Sleepy and fell off bridge. *Hall v. Progressive Life Ins. Co.*, 61 Ga. A. 792, 7 S. E. (2d) 606 (1940). The length of the deceased's arms may disprove suicide by a shotgun wound. *Pythias Knights' Supreme Lodge v. Beck*, 181 U. S. 49, 21 S. Ct. 532, 45 L. Ed. 741 (1900) is illustrative of one of many such cases.

⁵⁹ *Lennox, W. G.*: Amnesia, real and feigned, *Am. Jr. Psychiat.*, 1943, xcix, 732; *Smith, Hubert W.*: Scientific proof and relations of law and medicine, *Clinics*, 1943, i, 1353.

⁶⁰ A curious but too frequent result of imperfect reporting in medical literature is illustrated by the article of Robert Richards, a lecturer in Forensic Medicine at the University of Aberdeen in Scotland, published in 1934 in the *British Med. Jr.*, i, 331. He proposed the theory of "automatism" to explain three cases in which patients later claimed that they emptied a bottle of barbiturates without remembering having done so. This theory, derived from inadequate data and without questioning the motives of these patients who may have been concealing an unsuccessful suicide, was eagerly picked up by other writers anxious to condemn barbiturates and soon became a medical fact, though not a single other such case has been reported since! Enough writers repeated the generalization of Richards to place the theory, unquestioned, in several good books on pharmacology. (How frequently has this happened in medicine?) Ten years later it became the plaintiff's theory in a suit for accidental death benefits. *Feldmann v. Conn. Mut. Life Ins. Co.* (C. C. A. 8, Mo.), 142 F. (2d) 628 (1944). On the first trial the jury found that the death was accidental, not suicidal, but the result of a "poison," an excepted risk. Judgment for the defendant was reversed because the trial judge failed to define "poison." A retrial resulted in a finding that the insured died of heart disease—not accident, suicide or poison, and the beneficiary did not appeal. The barbiturates are fast becoming a popular method of suicide, although, fortunately, many attempts are unsuccessful because the victim usually falls into a deep coma which may last several days before death ensues, and during this time picrotoxin and other drugs stimulating the higher centers may be administered. It would be unfortunate if the unfounded assumptions of Richards, who borrowed the favorite defense of "automatism" from criminal lawyers to excuse attempted suicides by barbiturates, should gain further currency in legal medicine.

⁶¹ *Christensen v. New England Mutual Life Ins. Co.*, 71 Ga. A. 393, 31 S. E. (2d) 214 (1944), s. c., 197 Ga. 807, 30 S. E. (2d) 471, s. c. (unreported, Ga. A.), 9 CCH Life Cases 268.

Occasion to Use the Lethal Agency. The jury will want to know whether the insured was on a hunting trip or cleaning his gun at the time of its discharge. Did he even intend to go hunting and could that be why he happened to be dragging it from the closet at the time it accidentally went off in his *mouth*?⁶² Was the deceased addicted to laudanum, an overdose of which killed him, and did he think that he was drinking wine?⁶³ Why was the gas stove unlit—had the deceased been using it to cook? Where was he going and for what reason was he driving back and forth across the railroad track,⁶⁴ or parked nearby until just before the train arrived,⁶⁵ or sitting on the rail?⁶⁶

The Time and Place of the Act. Most suicides are committed in secluded places, in the basement, attic, bathroom, lying in bed, behind locked doors, in the garage or woods, etc.⁶⁷ A time and place is chosen when the attempt will not be arrested, and so that the deed will not be uncovered until after resuscitation would be useless. By carefully tracing the movements of the deceased, one may deduce the plan and intention which led up to the act. On the other hand, a similar tracking of his actions may point to the fact that the deceased desired, intended and definitely planned to live beyond the fatal moment of an accidental death.

3. Subsequent Evidence

Conduct of the Deceased. If the deceased accidentally swallowed lysol, he surely would have cried out and sought help because his mistake would have been known immediately.⁶⁸ Sometimes the mortally wounded suicide will readily admit what he has done. Others refuse to talk. Still others may claim that it was accidental. Any statement or refusal to talk or indifference to the then known harm, or effort to prevent resuscitation may be proved to show that the act was either suicidal or unintentional.⁶⁹

Conduct and Statements of Others. Relatives of the deceased will often disclose methods, motives, previous attempts and other valuable evidence

⁶² This was the famous case of *N. Y. Life Ins. Co. v. Gamer* (C. C. A. 9, Mont.), 76 F. (2d) 543 (1935), s. c. (C. C. A. 9, Mont.), 90 F. (2d) 817 (1937), s. c. 303 U. S. 161, 38 S. Ct. 500, 82 L. Ed. 726 (1938), s. c. (C. C. A. 9, Mont.), 106 F. (2d) 375 (1939), s. c. 308 U. S. 621, 60 S. Ct. 294, 84 L. Ed. 518 (1939).

⁶³ *Ingersoll v. Knights of Golden Rule* (C. C., Ga.), 47 Fed. 272 (1891).

⁶⁴ *Aetna Life Ins. Co. v. Newbern* (C. C. A. 8, Ark.), 127 F. (2d) 171 (1942).

⁶⁵ *Aydelotte v. Met. Life Ins. Co.*, 124 N. J. L. 266, 11 A. (2d) 122 (1940).

⁶⁶ *Dixon v. Met. Life Ins. Co.*, 136 Pa. S. 573, 7 A. (2d) 549 (1939).

⁶⁷ So also it may be important to consider that the deceased did not bide his time, but was killed before witnesses, indicating, possibly, an accident. *Oubre v. Mutual Life Ins. Co. of N. Y. (La. A.)*, 21 So. (2d) 191 (1945).

⁶⁸ *Lindblom v. Met. Life Ins. Co.*, 210 App. Div. 177, 205 N. Y. S. 505 (1924). "The odor, taste and burning quality were sufficient to enable decedent to identify the acid and quickly emit it if accidentally taken, and yet a considerable quantity of it was found in his stomach." *Carroll v. Prud. Ins. Co.*, 125 N. J. L. 397, 15 A. (2d) 810 (1940).

⁶⁹ *Hamilton v. Met. Life Ins. Co.*, 71 Ga. A. 784, 32 S. E. (2d) 540 (1944). On the other hand, the deceased may have sought assistance and then have been cooperative and hopeful of recovery, indicating accident. *Union Central Life Ins. Co. v. Cooper* (C. C. A. 5, Ala.), 115 F. (2d) 222 (1940); *Walker v. Prud. Ins. Co.* (C. C. A. 5, Fla.), 127 F. (2d) 938 (1942).

shortly after a suicide and before the advantages of silence are fully known. Any statement of an interested party to a subsequent claim may be admitted in evidence as an admission against interest. Statements to police, newspaper reporters, friends, the undertaker and the coroner may be checked for this type of evidence.⁷⁰ Proofs submitted to an insurance company signed by the beneficiary or by an attending physician or containing a copy of the coroner's verdict are admissible as the beneficiary's admissions against interest.⁷¹ They are not admissible when offered in evidence by the beneficiary because they are hearsay and self-serving declarations. Sometimes the interested party may attempt to conceal evidence or will refrain from producing it, though available to such party alone. In such case a legitimate inference of fact (evidence) arises that the evidence would be unfavorable to that party.

Death Certificates and Coroners' Verdicts. We have mentioned that in many states the death certificate is *prima facie* evidence of the *facts* therein contained.⁷² This may or may not permit the introduction in evidence of the death certificate to show the signer's *belief* that the death was "probably" accidental or suicidal, or, if suicidal, "due to a temporary mental aberration."

Almost all states have ruled that the coroner's verdict is not admissible in evidence because it is *ex parte* and hearsay. An exception exists where the inquest verdict is voluntarily made a part of the proofs submitted to the company and was not required by it. As previously shown, the verdict in such a case is admissible against the beneficiary, but not in his or her favor, because it was made a part of her own proofs to the company.

V

SPECIFIC PROBLEMS RELATED TO VARIOUS VIOLENT DEATHS

The choice of method and the rate of suicide vary widely according to age, sex, race, nationality, rural or urban nature of the population, geographical area, and several other factors. There also seems to be some discrepancy between the figures reported by various compilers of statistics. No single case can be determined by statistical probabilities or the "average" case or what "usually" happens, because in the whole field of this problem there is

⁷⁰ A doctor or other witness, expert or lay, cannot testify that in his opinion the death was accidental or suicidal because that would invade the province of the jury on an ultimate issue. *Cooley*, vol. 6, p. 5472; *N. Y. Life Ins. Co. v. Ittner*, 62 Ga. A. 31, 8 S. E. (2d) 582 (1940), ruling, however, that any witness in a position to know may testify that in his opinion the wound could or could not have been self-inflicted; *Furbush v. Maryland Casualty Co.*, 131 Mich. 234, 91 N. W. 135 (1902), opinion that deceased was murdered.

⁷¹ *Gordon v. Mutual Life Ins. Co. of N. Y. (D. C., La.)* 37 F. Supp. 873 (1941); *Cooley*, vol. 6, pp. 5466, 5477. Proofs are not conclusive if explained as made under great stress and emotion, without reading them, under misapprehension of the facts or in ignorance of material matters subsequently ascertained. *Ibid.* Proofs made to other companies are also admissible. This source of information is frequently lucrative, but is often neglected by investigators. *Fleetwood v. Pacific Mutual Life Insurance Co.*, 246 Ala. 571, 21 So. (2d) 696 (1945).

⁷² 17 A. L. R. 359; 42 A. L. R. 1454; 96 A. L. R. 324; *Couch*, vol. 8, p. 7232; *Cooley*, vol. 6, p. 5466 ff.

almost no general rule without its exceptions,⁷³ and, more important, the court will not admit this type of evidence since the court is concerned only with the case on trial.

It is the almost unanimous opinion of medical jurists, with whom we concur, that except in the case of suicide by firearms the medical jurist is of little practical assistance in determining whether any one death was accidental or suicidal.⁷⁴ In other words, in over two-thirds of all cases of violent death where the ultimate decision is suicide, that opinion or finding must depend almost entirely upon other evidence than that of the medical witness, with very few exceptions, and *assuming, of course, that the physical cause of death has been established*. That assumption we carry forward into and throughout the following discussion of evidentiary aids in distinguishing between accident and suicide, according to the cause of the violent death.

A

GUNSHOT WOUNDS

1. *What Was the Occasion for Use of the Gun?*

This topic as a general subject of inquiry in all cases was discussed in IV, B, 2, *supra*. It may be important to determine whether the deceased

⁷³ "The method of his exit from life was certainly unusual, but the instances are legion of one determined to die seeking strange or bizarre methods of encompassing death." *Home Life Ins. Co. v. Moon* (C. C. A. 4, W. Va.) 110 F. (2d) 184 (1940).

⁷⁴ If this paper has any value at all it will be in verifying this statement which appears in authoritative sources in general form and in specific reference to various types of violent deaths. We cite here the general statements and will footnote more specific conclusions as each method of suicide is examined. Webster terms the medical evidence as "absolutely necessary" (p. 157) in determining the answer to the question of accident, suicide, or homicide, but cautions that "many of the circumstances are such that the medical witness must know them before he is in a proper position to bear just witness as to the facts" (p. 151). Glaister regards the "whole general question of wounding with respect to accidental suicidal or homicidal causation . . . a field . . . too wide . . . to permit of the statement of such guiding principles as might be of absolute value to the student" (p. 381) ". . . all that can be said is, that the whole circumstances of the wounding, and the environment of the body when found, must be completely observed, considered, and weighed, before a pronouncement of opinion is made . . ." (p. 389). Gonzales states that "accidental deaths can be diagnosed only from the circumstances of the case combined with the results obtained at autopsy" (p. 5) but notes that "it is not possible in all cases to say whether death is homicidal, suicidal or accidental" (p. 108). According to Smith, "the final question . . . can be decided only after a careful consideration of the whole of the facts as well as of any statements made by witnesses" (p. 124). Kerr considers the evidence relating to the circumstances of the death "just as important as the actual violence found on the body" (p. 93). Ewell concluded that "whether [wounds] are suicidal, accidental or homicidal is frequently impossible to determine; and when it can be determined, must depend upon the application of the ordinary rules of evidence and not upon the medical expert." Ewell, M. D.: *A Manual of Medical Jurisprudence*, ed. 2, 1909, Little, Brown & Co., Boston. See also: Herzog, pp. 280, 286.

Among the writers of the last century Taylor commented that "we cannot always obtain certainty in a question of this kind—the facts will often allow us to speak only with different degrees of probability" (p. 266). "Circumstantial evidence is commonly sufficient to show whether a wound has been received accidentally or not; but as an accidental wound may sometimes resemble one of homicidal or suicidal origin, so it follows that it is not always possible for a medical jurist to decide the question peremptorily from a mere inspection of the wound" (p. 270). See also: Wharton & Stillé, vol. 2, p. 672; Witthaus & Becker, vol. 2, p. 72, 94.

was hunting or even said that he intended to go hunting, or usually carried a gun with him, or was cleaning or repairing or wrapping the gun, or said that he intended to do so.⁷⁵ The number of shells exploded and unexploded, in the gun or nearby may indicate that the deceased was loading or unloading the gun or thought that the gun was unloaded, or on the other hand, had deliberately loaded the gun for self-destruction. If he was twirling the gun⁷⁶ or "pranking" with it⁷⁷ or demonstrating how another had committed suicide⁷⁸ or was playing "Russian roulette,"⁷⁹ then the occasion for the use of the gun would not be for the purpose of suicide, and the inference and conclusion of accident might be drawn. On the other hand, the proponent of the suicide theory will endeavor to show that there was no occasion other than suicide to use the firearm, that no rags or cleaning equipment were near, that no hunting trip was under way or proposed, that the gun was evidently deliberately loaded and discharged, or that the deceased bought, borrowed or assembled the gun for no other apparent purpose.

2. Who or What Discharged the Gun?

In favor of the theory of accident it may be shown that the gun was old, rusty, "tricky" or "easy on the trigger," had no safety device or a defective one, could be (by tests)⁸⁰ and had been (from previous experience) dis-

⁷⁵ Walker v. Prud. Ins. Co. (C. C. A. 5, Fla.) 127 F. (2d) 938 (1942); Lewis v. N. Y. Life Ins. Co., 113 Mont. 151, 124 P. (2d) 579 (1942); Mut. Life Ins. Co. v. Graves (C. C. A. 3, Pa.) 25 F. (2d) 705 (1928). In one case the insured, former mayor of his town, was under indictment for embezzlement and had far-advanced cancer of the throat and mouth affecting his speech, hearing and sight. One afternoon he locked himself in the bathroom, clad in his pajamas, with an Iver-Johnson revolver which had not been used for years. It could not be discharged except by pulling the trigger. A shot sounded and he later unlocked the door, walked to a bed and collapsed with a contact wound just under his heart. There was no hole in the pajamas. The court held that there was sufficient evidence of accident, because, among other things, he shot himself only once, did not inflict a wound which would immediately kill himself, did not admit that he had attempted to commit suicide, and (of all reasons) there was a dust rag nearby and it was the 4th of July so he might have been cleaning the gun preparatory to celebrating the American Holiday, a practice the court judiciously noticed! Edwards v. Business Men's Assur. Co., 350 Mo. 666, 168 S. W. (2d) 82 (1943). This was the case in which the plaintiff was permitted to submit her case to the jury without electing between the two alternative theories pleaded: (1) that insured accidentally discharged the gun, or (2) purposely did so to commit suicide but while insane. An osteopath's testimony that in his opinion the insured's mind was "unsound" was considered substantial evidence of insanity. The jury returned a verdict for the defendant.

⁷⁶ N. Y. Life Ins. Co. v. Sparkman (C. C. A. 5, Fla.) 101 F. (2d) 484 (1939).

⁷⁷ Met. Life Ins. Co. v. Graves, 201 Ark. 189, 143 S. W. (2d) 1102 (1943).

⁷⁸ Aetna Life Ins. Co. v. Kent (C. C. A. 6, Mich.) 73 F. (2d) 685 (1934). In this case a lawyer was showing a friend how he had defended a man charged with murder by contending that the deceased committed suicide. He placed the gun to his head, said it was not loaded, pulled the trigger and killed himself. Accident or suicide? The court found evidence in favor of both theories and affirmed the finding of the jury for the beneficiary.

⁷⁹ Pac. Mut. Life Ins. Co. v. Fagan, 292 Ky. 533, 166 S. W. (2d) 1007 (1942).

⁸⁰ Brown v. Met. Life Ins. Co., 233 Ia. 5, 7 N. W. (2d) 21 (1942); Scales v. Prud. Ins. Co. (C. C. A. 5, Fla.) 109 F. (2d) 119 (1940); Love v. N. Y. Life Ins. Co. (C. C. A. 5, Miss.) 64 F. (2d) 829 (1933). In the case of Downing v. Met. Life Ins. Co., 314 Ill. A. 222, 41 N. E. (2d) 297 (1941) the court affirmed a verdict for plaintiff holding that tests at the scene near a fence to determine whether a shotgun could have been purposely discharged by the deceased were admissible. However, the court said: "It must be emphasized that evidence of tests or experiments should be received with caution by the trial judge and admitted only where it is certain that they were conducted under circumstances very similar

charged in a variety of ways without pulling the trigger (as by dropping, striking the butt on the floor, striking the hammer or breech, catching the trigger, etc.). The type and make of the firearm are important, it being well known that some guns are much easier to fire accidentally than others.⁸¹ Scratches or marks on surrounding objects may indicate that the gun scraped or struck the object, and the gun itself may have an imprint favoring this theory. The presence of a large number of sticks nearby a man killed by a long-barreled shotgun would destroy part of the inference that he used any one particular stick to push the trigger. So also if his shoes were too large to push the trigger with the toe and if the barrel of the gun was too long for him to reach the trigger, an inference of accident may well arise, there being no pencil, stick or other object nearby with which the deceased could have done the deed. In several cases it has been shown that the gun was fired in a closet where it was left and where it might have become caught on clothes or struck against something to fire it. In other cases the death occurred near a fence or bush or where the deceased or the gun was in position making it awkward for him to handle it and increasing the possibility of its accidental discharge. It may be shown that the gun customarily left "powder burns" on the hand and that there were none on that of the deceased, or that there was a bruise on the hand indicating that he had struck it against something while holding the weapon. In several cases inferences of accident were drawn where the gun might have fallen from or been discharged during removal from a glove compartment of a car, or while on or near the seat of a car, or on a shelf where it was customarily kept.

The deceased may also have had some physical impairment or been subject to "fainting fits" and these facts have been considered proper as increasing the possibility of accident.

In favor of the theory of suicide, it has been shown and considered as proper evidence upon which, with other facts, to raise an inference of self-destruction that the gun was in good condition, required a heavy pull on the trigger, had a safety device or well-guarded trigger, could not be (by tests) and had never been (from experience) accidentally discharged, required grasping of the handle to release a safety, or required a cock and pull of the trigger to fire it. A search of the scene may disclose, generally, no signs of

to those connected with the act to be illustrated thereby." In another case the coroner conducted tests to duplicate "powder burns" found on the deceased and then testified that the gun was at least 13 inches away from the body when discharged. The evidence was admitted over defendant's protest that there was a difference in the cartridges used in the tests and that marks left on paper are different from those on flesh. *Lewis v. N. Y. Life Ins. Co.*, 113 Mont. 151, 124 P. (2d) 579 (1942). Both objections would seem to be valid, except that most authorities on powder marks illustrate their contentions by tests on paper and other inanimate material. Such tests will fairly well duplicate the presence and diameter of powder marks, tattooing, etc. and may be valid, but for that purpose only. The subject requires a more elaborate study than any we have yet found. See: 8 A. L. R. 18; 85 A. L. R. 47. A good example of the impropriety of tests is illustrated in the *Gamer* case, f. n. 62, supra.

⁸¹ Hatcher, p. 211 et seq. It is possible to remove the magazine of an automatic revolver and forget that a bullet is left in the chamber. See testimony in *McLane v. Reliance Life Ins. Co.*, 192 S. C. 245, 6 S. E. (2d) 13 (1939).

a scuffle or accident or tripping or striking or dropping of the firearm. A recoil mark of a shotgun butt on the ground or floor may point to suicide. If the shotgun barrel was short enough to permit the deceased to reach the trigger, the length of the arms of the deceased should be measured. Many cases come to court without such evidence, and the parties are forced to rely upon such weak evidence as the testimony of a tailor, or that of a relative or friend who tells the jury that the arms of the decedent were "as long as his." The finding of a pencil or stick held in the hand of the deceased is a good sign of suicide where a shotgun has been used, but is not conclusive. The pencil, stick or other object should always be sought and preserved as evidence. The suicide may have occurred in an open place where it could not easily have been caught on anything. A large number of other cases seem to occur while the deceased was lying down on the floor or in bed. The relative positions of the gun, an ejected cartridge, and the body and its extremities may indicate that the deceased either suffered an accident or pulled the trigger himself with intention to end his life, and much evidence of this type is received. It is of questionable value in many cases because of the movements of the body after the shot is fired.

3. Did the Deceased Know of the Danger Imminent?

The fact that the deceased knew how to use and handle firearms and knew the dangers involved may be argued both for and against suicide. Of more importance is a determination of whether he knew that the gun was loaded. In some cases it can be shown that the deceased probably did not know that a shell was in the weapon while in other cases the opposite can be proved by direct or circumstantial evidence.⁸²

Where the deceased is found with more than one self-inflicted gunshot wound, or where there are "snapped" but unfired shells next to the exploded cartridge, then it should be strongly inferred that the deceased knew that the gun was loaded, and that he deliberately pulled the trigger with the gun turned upon himself.⁸³

⁸² *Tully v. Prud. Ins. Co.*, 234 Wis. 549, 291 N. W. 804 (1940). A borderline case is that of *Pac. Mut. Life Ins. Co. v. Fagan*, 292 Ky. 533, 166 S. W. (2d) 1007 (1942) where deceased "unloaded" a pistol with nine chambers, shortly thereafter demonstrated how the Russians played "roulette" with death and lost the game, falling with a "surprised" look on his face. There were two more unexploded shells found in the gun.

⁸³ *Central States Life Ins. Co. v. McElwee*, 199 Ark. 410, 133 S. W. (2d) 881 (1939), where the insured fired five shots, three of them entering his left chest in a three inch circle. The court said: "No reasonable man could conclude that McElwee shot himself accidentally five times at intervals of a minute or more." And see: *Domanowski v. Prud. Ins. Co.*, 116 N. J. L. 247, 182 Atl. 906 (1936); *Cruse v. Union Central Life Ins. Co.* (D. C., Tex.) 59 F. Supp. 504 (1945). In the last case cited the medical testimony was in conflict whether it was physically possible for a man to shoot himself in or near the heart five or six times. The experts for the plaintiff seemed to ignore the fact that an eyewitness entered the room and found the insured on the floor attempting to draw the hammer back on the gun. He lived for 30 minutes until he reached the hospital. Anyone who reads very far into reliably reported cases of violent wounds will find that the slightest blow may render a person unconscious or kill him, while in other cases unbelievably severe injuries may still be consistent with consciousness, voluntary movement and complete recovery.

4. *Where Was the Gun When Fired?*

This is an inquiry in which scientific evidence offers substantial aid.

The general considerations that are recommended for all types of medico-legal inquiry into violent death apply in this instance also, since the evidentiary aid of scientific data relating to the use of firearms alone will not determine whether or not a gunshot wound was inflicted intentionally by the deceased or another person.

The following discussion, so far as it relates to scientific determinations of the location of the gun when fired, is, for the most part, drawn from several recent and reliable authorities which may be found in the Additional References to this paper.⁸⁴ So far as the reported cases of law are concerned, the witnesses, lay and expert, the lawyers, the judges and the juries seem to have been hopelessly confused. A powder mark of one description will not only receive different interpretations in the same case, but will be taken to have exactly opposite meaning in another case. Descriptions are inaccurate and conflicting. Unqualified witnesses pass themselves off as experts. The result would justify the deriding criticism of Jeremy Bentham in 1827: "Good evidence excluded—bad received! Jargon without end—fiction without shame." This will ever be the result until Scientific Proof whips the lying, ignorant witness, the money changing expert and the pettifogging lawyer from the temple of justice.

(a) *Physical Findings*

General Considerations. Since a gun cannot be intentionally fired upon one's self when held with the muzzle over 24 inches away, it becomes necessary to determine the type of a wound which may be caused by the particular firearm and cartridge used when such a gun is held *over* two feet from the body. On the other hand, even where the gun muzzle is found to have been *within* two feet of the body, that fact by no means proves that the deceased either fired the gun, or intentionally did so, or (the ultimate question) pulled the trigger intending to kill himself.

The scientific considerations are in part physical, and in part chemical and photographic. A combination of all three types presents the most conclusive form of scientific evidence and the least likelihood of controversy.⁸⁵

Location of the Entrance Wound. In some cases the absence of holes or powder marks on the garments will indicate, as so often happens, that the deceased drew his clothes aside in order to place the gun against his body. The apparent purpose: to be certain to hit a vital spot. So also the clothes

⁸⁴ Walker, pp. 500-519; Moritz, pp. 43-66; Vande Grift pp. 423-430; Hatcher, pp. 200-228; Snyder, pp. 55-123. Other references will be footnoted.

⁸⁵ For the means by which Scientific Proof is designed to eliminate error and to secure truth, see Smith, H. W.: Components of Proof in Legal Proceedings, 51 Yale L. J. 537, 1942. One of these is "the use of all appropriate methods of corroboration, with accent on diverse sources and types of evidence." Another is "the eventual grading of all types of evidence according to relative probative value." And another is "the development of usable criteria and safeguards in respect to each type of evidence."

may become ignited or bear evidence of a burn or powder marks at the site of the entrance wound and thus give evidence of a close range of fire.⁸⁶

A renewed word of caution: the mere fact that a wound was self-inflicted does not prove that it was intentionally inflicted for the purpose of *felo-de-se*. And, as noted, the trigger of a gun may even be intentionally pulled while the firearm is aimed at a vital spot of the body and yet the intention to commit suicide may be totally lacking.⁸⁷ On the other hand, the mere fact that a self-inflicted gunshot wound is found over or near a vital spot of the body raises a strong suspicion of suicide, increasing to a probability where the gun is found to have been held against or in close proximity to the body.⁸⁸ In such cases the path of the bullet or shot is usually straight in and through, and, to achieve that end the suicide in some cases will be found in front of a mirror which he used the better to direct the projectile and so successfully to accomplish his purpose.

One writer states that as many as 62 per cent of all suicidal gunshot wounds are found with the entrance in the mouth,⁸⁹ but this percentage is not supported by the experience of others.⁹⁰ Such wounds are almost conclusive evidence of suicide, and some courts so hold, but the exceptional case which may always be found may be raised to plague the judge.⁹¹ These observa-

⁸⁶ Proctor v. Preferred Acc. Ins. Co. (C. C. A. 6, Ky.) 51 F. (2d) 15 (1931); Knapczyk v. Met. Life Ins. Co., 321 Ill. A. 611, 53 N. E. (2d) 484 (1944). Compare Tabor v. Mut. Life Ins. Co. of N. Y. (C. C. A. 2, W. Va.) 13 F. (2d) 765 (1926). In one case the appellate court examined the pajamas and bathrobe of the deceased and reached its own inexpert conclusion concerning what were powder marks and what was grease, disagreeing with some of the witnesses, and concluding that from what it found the jury could have concluded that the deceased was shot in the back! Mo. State Life Ins. Co. v. West (C. C. A. 10, Okla.) 67 F. (2d) 468 (1933).

⁸⁷ The lawyer demonstrating how another man committed suicide. Aetna Life Ins. Co. v. Kent (C. C. A. 6, Mich.), 73 F. (2d) 685 (1934).

⁸⁸ "The nature of the wound itself bars any reasonable hypothesis of accident." Mitchell v. New Eng. Mut. Life Ins. Co. (C. C. A. 4, Va.), 123 F. (2d) 246 (1941). But such a finding is not controlling or conclusive. Scott v. Prud. Ins. Co., 203 Minn. 547, 282 N. W. 467 (1938).

⁸⁹ Hatcher, p. 209. This writer also says that 18 per cent of all suicidal gunshot wounds are in the temple.

⁹⁰ Snyder, p. 80, says that the majority of such wounds are found in the right temple, with wounds in the mouth next most common. One coroner testified in a case for the beneficiary, whose husband was found with a pistol wound below his heart, that in 3½ years he had investigated 500 suicides. One-half of these died by gunshot wounds and all of those, except one, were in the head! Sutcliffe v. Iowa State Trav. Men's Assoc., 119 Ia. 220, 93 N. W. 90 (1903). Such "statistical" evidence is not admissible because it does not prove the cause of death in the case on trial. The amazing thing is that while courts will stoutly adhere to this rule excluding statistical evidence, they will continue to manufacture their own evidence by "judicial notice" of the most unbelievable and scientifically untrue things. They will also indulge in presumptions to assist a party without evidence which the burden of proof requires him to produce. The criticism of Judge Felton, dissenting in N. Y. Life Ins. Co. v. Ittner, 64 Ga. A. 806 14 S. E. (2d) 203 (1941) will ultimately be justified by historical, statistical, and other scientific proof. He said: "It will be seen, upon consideration, that the presumption against suicide does not owe its existence to facts having evidential value. What most people do or do not do has no bearing whatever on whether one particular individual committed suicide or was killed accidentally. . . . That most people love life too well to destroy it is not a fact about the deceased from which the presumption springs."

⁹¹ Gamer v. N. Y. Life Ins. Co., f. n. 62, supra, where an abrasion on the lip was, with other slight evidence, sufficient to permit the jury to guess that the rifle accidentally rammed into the deceased's mouth. It was also pointed out that his artificial upper plate would offer no resistance to such an accident.

tions are but one phase of the general rule that suicides seek to reach a vital organ with as little pain or suffering to themselves as possible, and the corollary: a self-inflicted wound to a vital part is presumptive evidence of suicide.⁹²

Size and Shape of the Wound. Entrance wounds may be round, oval, elliptical, lacerated or linear, depending on the position of the bullet at the moment it strikes the target and whether or not the muzzle of the gun is in contact with the target. Large, lacerated entrance wounds are associated generally with contact shots, but in gunshot wounds other than contact shots the entrance wound is usually smaller than the exit. No conclusion is warranted as to the caliber of the bullet merely from the size and shape of the wound. Exit wounds produced by projectiles discharged from firearms are more irregular than entrance wounds and characteristically show lacerations extending beyond the margins of the central defect. Exit wounds will not show any burning, bruising, abrading or deposit of metal, smoke or powder. The presence of foreign particles beneath the skin or within the wound will serve to distinguish large contact wounds with lacerations from exit wounds.

Burning, Bruising, and Abrading of the Entrance Wound. Earlier writers referred to burning of the entrance wound as "the brand." It is occasionally termed "scorching" and sometimes "singeing." The burning will vary in degree and extent depending upon the type of powder charge and the position of the muzzle at the time of firing.

The margins of the skin entered by firearms projectiles are invariably bruised and abraded regardless of the distance from which the projectile is fired. In the event that the muzzle of the weapon is in contact with the skin, a "bruise-pattern" or "stamp mark" of the muzzle, the sight, the ejector slide or the retractor spring rod may be imprinted on the target, depending on individual features of the gun.⁹³ Metallic particles or lubricant derived from the bullet frequently adhere to the margins of the entrance defect. This is called the "contact ring."

Deposits of Gaseous Combustion Products, Metallic Particles and Powder Residues, etc., Within and About the Entrance Wound. Various

⁹² Evidence of the location of the wound takes on added significance when it is considered that suicidal wounds of the head in left-handed persons are found in the left side of the head. *Frankel v. N. Y. Life Ins. Co.* (C. C. A. 10, Okla.), 51 F. (2d) 933 (1931); *Mut. Life Ins. Co. of N. Y. v. Hatton* (C. C. A. 8, Ia.), 17 F. (2d) 889 (1927); *N. Y. Life Ins. Co. v. Bradshaw* (C. C. A. 5, Ga.), 2 F. (2d) 457 (1924). Compare: *Jovich v. Benefit Assoc. of Ry. Employees*, 211 Ia. 945, 265 N. W. 632 (1936). A wound on the left side of the head in a right-handed person is said to indicate accident or homicide, not suicide. *Aetna Life Ins. Co. v. Milward*, 118 Ky. 716, 82 S. W. 364 (1904). Compare: *Inghram v. Nat'l Union*, 103 Ia. 395; 72 N. W. 559 (1897). In *Edwards v. Business Men's Assur. Co.*, 350 Mo. 666, 168 S. W. (2d) 82, the deceased shot himself just below the heart. The court, in holding that there was substantial evidence of accident asked, "If the insured intended to commit suicide because of the motives referred to by respondent, why was a wound inflicted that would not produce immediate death?" To which one might reply: "How does the court know that the insured knew the exact location of his heart?" Few laymen realize the high location of the heart and the fact that one-third of it is to the right of the midline.

⁹³ See photographic illustrations in *Gonzales*, pp. 232-233; *Snyder*, p. 66. This fact is seldom revealed to the jury, because it is not carefully noted or is misinterpreted as a part of powder burns. See: *Burkett v. N. Y. Life Ins. Co.* (C. C. A. 5, Miss.), 56 F. (2d) 105 (1932); *Aetna Life Ins. Co. v. Tooley*, (C. C. A. 5, Tex.) 16 F. (2d) 243 (1926).

deposits of smoke, metal and powder about entrance wounds have received numerous terms, such as "tattooing," "smudging," "stippling," "fouling," "smoke halo," "powder marking," and "powder residue pattern." In legal proceedings the general phrase "powder burns" is used indiscriminately by doctors, lawyers, witnesses and the courts to apply to any markings observed, without distinguishing between burning, bruising, and the deposit of foreign material. The terms "tattooing," "stippling," "powder marking" and "powder residue pattern" generally refer to the presence of imbedded grains of powder and particles of metal within the target. "Smudging" and "smoke halo" are names generally applied to the deposit on the target of a fine, black or gray dust or soot containing carbon and metals. Moritz uses the name "fouling" to include both "stippling" by powder and "blackening" by smoke. Hatcher speaks of a "powder brand" in referring to eccentric deposits of powder residue or to dissimilar degrees of burning about the wound. In addition to foreign material derived from the ammunition and gun and deposited upon the target, entrance wounds of skin may also show particles of fabric or hair.

(b) Chemical, Photographic and Microscopic Method

Ordinary examination under the microscope of foreign materials removed from the surface or subsurface of the wound will serve often to identify characteristic substances such as metal, powder, hair or fabric. Radiographic, spectrographic and microchemical methods are not yet suited to general use, but in the hands of experts the results of such studies are invaluable. The other methods noted provide adequate and useful results for general medico-legal investigations and civil proceedings.

Infra-red Photography. Photographs prepared with infra-red sensitive film and infra-red filters will demonstrate not only the presence of a contact ring but will provide also a permanent record of the distribution of combustion residues about the entrance defect. Blood will not interfere with the results if the proper filter is used.

Macrochemical Tests. Walker has shown that powder residues tested with "C" acid (2-naphthylamine) will give characteristic results highly indicative of the presence of such substances. In the case of fabrics the results can be shown in the form of a permanent imprint upon specially treated ordinary photographic paper. In the instance of skin wounds, Moritz suggests the use of paraffin casts of the entrance wound. Melted paraffin is applied to the wound in combination with layers of gauze. When the hardened paraffin and gauze is removed, most of the material deposited on the skin will adhere to the cast. This in turn may be tested with "C" acid.

(c) Direction of the Tract

In establishing the direction of the bullet tract autopsy studies should be preceded by and combined with photographic representations showing probes

linking both exit and entrance wounds and protruding from each. In the absence of an exit wound probes must be used with caution since false tracts may be created. The results of determining the direction of the tract are not suitable for establishing all of the circumstances of the shooting but, as Moritz points out, serve a useful purpose in confirming or impeaching the testimony of witnesses. Courts have impliedly in many cases and explicitly in others recognized that where a pistol is discharged away from the body there is less likelihood of a direction through the body perpendicular to the surface of entrance than where the gun is held close to or against the body for the purpose of suicide.⁹⁴ So also, if the gun is dropped and accidentally fired, it would be almost impossible to produce a wound in the temple straight through the head from one side to another. Therefore, in reconstructing the events attending the discharge of the gun, the position of the deceased as established by the path of the bullet in the body and after it leaves the body may show that the gun was held and discharged in such a way as to indicate a suicide.

(d) Angle of Fire

A shot cannot enter the body where the angle of incidence is 5° to 10° or less. The shape of the wound may offer some clue to the angle of fire. Thus, angular shots are associated frequently with linear or ovoid wounds; the near side may show abrasion, the extent of which may be roughly proportional to the angle of incidence. Heavier deposits of gases and powder residue are anticipated generally at the near side of the entrance wound, a finding which can best be reproduced by infra-red photography. Other circumstances, however, may lead to a false impression of an angle shot. Several writers have called attention to the frequent eccentric deposit of powder, smoke and metal about the entrance wound in close-range shots, generally ascribed to the deflection of the gases discharged during the recoil of the gun. Should the weapon consistently produce an eccentric pattern with test shots, a basis is provided for an opinion regarding the position of the gun when fired.

(e) Range of Fire

The presence of burning, or the deposit of powder, metal or smoke about the bullet wound are general indications of a shot fired at close range.⁹⁵ In individual cases consideration must be given to the type of ammunition used, the type of gun, the construction of the gun, the type of target and the pos-

⁹⁴ On the other hand the location of the entrance wound and the course of the bullet may indicate that the deceased could have fired the shot intentionally only with difficulty and uncertain aim. *Cochran v. Mut. Life Ins. Co.* (C. C., Ore.), 79 Fed. 46 (1897). A suicide by holding the gun any considerable distance from the body is said to be an unusual and uncertain way to shoot one's self. *Hunt v. Ancient Order of Pyramids*, 105 Mo. A. 41, 78 S. W. 649 (1904).

⁹⁵ As we have noted, the opinions of courts indicate that, although there is much evidence about "powder burns" introduced in almost every case, there is a complete disagreement among witnesses upon both the presence and interpretation of such marks.

sibility of a discharge of the combustion residue and powder grains at the subsurface of the target, as for example in a perfect contact shot.⁹⁶ It is uniformly agreed by authorities that no specific conclusions regarding the range of fire are warranted until test shots have been made using the same gun, the same ammunition and the same type of target as were involved in the case under investigation.

It is possible, however, to make certain general statements regarding the range of fire indicated by the presence of certain features of the entrance wound. *Powder residue.* The deposit of powder residue from the discharge of black powder may occur at ranges of 3 to 6 feet or more, while smokeless powder may project none within a few inches of the target. *Metallic deposits.* Walker finds that molten lead derived from the discharged bullet could be detected in decreasing amounts up to 6 inches from the target but Moritz notes that particles of metal can be carried for a distance of several feet from the target. *Smoke.* Walker states that the products of combustion of smokeless powder generally have a range of 12 to 18 inches, while Snyder places it at 18 to 24 inches. Moritz makes the general statement that targets "less than 12 inches from the muzzle . . . will often be blackened by the smoke of the discharge." *Burning.* The range of fire indicated by burning of the target is said to extend rarely beyond 6 inches and to be present invariably at less than 3 inches (Moritz). It is agreed that with smokeless powder no burning may be observed at ranges of a few inches. According to Walker (following Weiman) "singeing" is observed generally with black powder charges at ranges of 8-12 inches, and sometimes at 20 inches. *Contact shots.* Infra-red photographs are well suited to the demonstration of patterned markings corresponding to features of the particular muzzle in contact with the target at the time of discharge. Observations tending to show extensive disruption of the subsurface of the target and the deposit of smoke, metals and powder within the wound rather than upon the surface serve to support the view that the muzzle of the gun

⁹⁶ Yet, many courts, after reviewing conflicting, confused evidence of lay and expert witnesses, probably agree with Judge Fox in *McDaniel v. Met. Life Ins. Co.*, 119 W. Va. 650, 195 S. E. 597 (1938): "The authorities on gunshot wounds do not lay down any inflexible or infallible rule as to the presence of powder burns in any case; whether they appear, and if so, to what extent, depends on the character of the gun used, the kind of powder, the distance from the body, and many other conditions and circumstances." See, also, cases collected in 17 Amer. & Eng. Anno. Cases 36, and Herzog, p. 241. In the case of *Gamer v. N. Y. Life Ins. Co.* (C. C. A. 9, Mont.) 76 F. (2d) 543 (1935), the court in dealing with a rifle wound in the mouth took judicial notice of ricochet phenomena and finally accounted for the location of a bullet hole in the ceiling. It assumed that the inside of the skull was a smooth surface, that the bullet struck at a slight angle, etc.! In the *McDaniel* case, *supra*, the pistol and unfired cartridges were turned over to a constable who later died, "and neither the pistol nor the cartridges could be located and produced at the trial." The bullet was found and turned over to a relative of the deceased but he died and that bit of evidence was not produced! The wound was washed by a physician and he "did not observe any powder marks." No inquest was held but the coroner in another state where the body was buried examined it for powder marks after it had been embalmed and prepared for burial. The plaintiff introduced evidence of tests made to show that "powder burns" would have been present if the insured committed suicide. The court, noting all of this, held that the only way that the jury could have reached a verdict for the plaintiff was by indulging in "conjecture and mere possibilities."

was pressed against the target at the moment of firing.⁹⁷ Blood found in the barrel or on the muzzle of a gun is evidence of a contact shot.⁹⁸ *Shotgun wounds.* Shotgun wounds will show the features of bullet wounds already described but in addition will be distinguished either by the presence of larger wounds where the gun is discharged within a range of 10 feet or by the characteristic dispersion pattern of the shot at greater ranges. In contact shots extensive disruption of the subsurface and even of entire body cavities is likely to occur. In contact shots of the head the entire skull, brain, and face may be distorted beyond recognition.

B

POISONING

Suicidal poisoning may result from the inhalation of gases, fumes or vapors, or from the taking of liquid or solid poisons by mouth. A death from carbon monoxide inhalation may or may not be a death from a "poison" or "poisoning" within the meaning of an exclusion in an insurance policy, since death usually results from anemic anoxia.⁹⁹

The medical witness, after once determining that death resulted from asphyxiation or poisoning, will be of little assistance in the determination of whether the death was accidental, suicidal or homicidal. Marks on the

⁹⁷ N. Y. Life Ins. Co. v. Newport, 1 Wash. (2d) 511, 96 P. (2d) 449 (1939), shotgun wad in the heart; Gordon v. Mut. Life Ins. Co. (D. C., La.), 37 F. Supp. 873 (1941); Travelers Ins. Co. v. Wilkes (C. C. A. 5, Fla.), 76 F. (2d) 701 (1935); Gorham v. Pac. Mut. Life Ins. Co. (C. C. A. 4, N. C.), 114 F. (2d) 97 (1940). In the Gorham case the autopsy physician concluded that the revolver wound to the head was a contact wound. "This was shown by the absence of branding or burning of the skin surrounding the wound, the presence of unexploded particles of powder in the brain where the bullet was found, and injury to the skull which could only be explained by the explosion within the skull of gases injected at the time of the shot. While there would be an absence of branding in the case of a shot made 12 inches or more from the head, as well as in the case of one made with the muzzle of the pistol pressed against the head, the presence of unexploded particles of powder within the wound and the injury to the skull from exploding gases could only be explained on the theory of a contact shot. The expert witness relied on by plaintiff was not present at the autopsy and had never so much as seen the body of the deceased or examined the wound or the condition within the skull. His testimony was entirely hypothetical and devoid of probative value." One interesting and repeated result of contact bullet wounds to the skull is a saggillation of blood around and beneath the eyes and, in some cases, in other parts of the skin or scalp. In one case where such marks were not explained to the court and jury it was held that they might indicate an assault preceding homicide, an accident in other words. On a second trial, these discolorations were explained on a scientific basis so that the court reversed the case outright, denying recovery despite the testimony of a gun expert that it was impossible for the deceased to have fired the gun himself and to have left no "powder burns," as disclosed by his tests! The two opinions in this case should be "required reading" for everyone interested in the problem under discussion. Bryan v. Aetna Life Ins. Co., 25 Tenn. A. 496, 160 S. W. (2d) 423 (1941), s. c. 174 Tenn. 602, 130 S. W. (2d) 85 (1939).

⁹⁸ Reliance Life Ins. Co. v. Burgess (C. C. A. 8, Mo.), 112 F. (2d) 234 (1940).

⁹⁹ Much of such evidence was received in the case of Cleaver v. Central States Life Ins. Co., 346 Mo. 548, 142 S. W. (2d) 474 (1940), and the court concluded that the question of whether carbon monoxide is a "poison" was one for the jury to decide. This decision should not be criticized until one has attempted for himself to obtain a satisfactory definition of "poison" from scientists or jurists. See 110 A. L. R. 1276; 131 A. L. R. 1061. When is a drug a "medicine" and when is it a "poison"? Is alcohol a poison? How about the barbiturates which have a lethal dose quantitatively less than numerous well-recognized poisons? Compare: Aubuchon v. Met. Life Ins. Co. (C. C. A. 8, Mo.) 142 F. (2d) 20 (1944) and Feldmann v. Conn. Mut. Life Ins. Co. (C. C. A. 8, Mo.) 142 F. (2d) 628 (1944).

body may indicate either an accidental fall or homicidal violence. ' Almost all other evidence aiding the jury will be non-medical testimony.

1. Asphyxiation

As far as statistics are reliable, it is found that suicide by carbon monoxide asphyxiation accounts for about 25 per cent of all suicides, and is the choice of method in urban centers.¹⁰⁰ The investigator should carefully note the position of the body with relation to the source of the gas and the presence or absence of methods of increasing its concentration or directing it into the deceased's lungs. The suicide is often found leaning over, upon or near a gas stove, and in one case had arranged a small pillow of cloth to make it more comfortable for him to place his forehead upon the grates. A blanket or shirt or other means may be devised as a hood to increase the concentration. Suicides in autos usually conduct the gas from the exhaust with a hose. The windows and doors of the room or car are found closed, and, in many instances small openings are blocked with rags, carpets or papers. More than one stopcock of a gas range will often be opened, and the absence of burnt matches nearby or the absence of cooking utensils on the stove will indicate that there was no accident. It is possible, of course, for the deceased to have fallen, from disease or accident, then to have struck the gas cock, opening it, and died of gas asphyxiation while unconscious from other causes.¹⁰¹ It may be possible, too, for the gas cock to have been opened unwittingly or accidentally by the deceased or others and then later, while sleeping, to have been overcome by the gas.

When the deceased is found in a garage dead from the inhalation of gas fumes, inquiry should disclose whether the doors had been shut or locked and for what reason. Was the motor still running, and how much gasoline had been consumed, and still remained? Was the ignition key on? Were there any tools lying around or near the deceased, and was there any grease on him? In other words, was there any indication that he was repairing the car? Occasionally it will be shown that the car needed repair, that deceased said he was going to repair it, etc.

It is possible to commit suicide by the inhalation of motor exhaust in the open without a hood by lying with the face close to the pipe.¹⁰² Because of the lack of expert evidence and scientific proof, the usual circumstantial evidence will fail clearly to demonstrate whether death was accidental or suicidal in most cases where the deceased is found dead from the inhalation of motor exhaust fumes. The smallest scraps of evidence will be used to sup-

¹⁰⁰ Cullen T. J. U.: War-time Prosperity Lowers Suicide Rate, *The Spectator* 151:8, 1943; Statistical Report of the Chief Medical Examiner of New York City, 1941, pp. 4-5; Report of the Maryland Post-Mortem Examiners Commission, Summary of Deaths, 1942; Annual Report of the Chief Medical Examiner of the County of Essex, N. J., 1942, p. 12; Annual Report on Vital Statistics of Mass., 1942, p. 212.

¹⁰¹ Herzog, p. 229. An analysis of a blood clot (hematoma) in the tissues for carbon monoxide will disclose whether the injury was received before or after the inhalation of the gas.

¹⁰² Snyder, p. 177, has photographic proof. See f. n. 103, *infra*.

port a theory of accident or homicide, and the courts seem reluctant to accept as conclusive even the strongest evidence of suicide.¹⁰³

2. *Liquid and Solid Poisons*

(a) In what form and manner was the poison taken into the body?

The investigator, medical and non-medical, should first determine if poison caused death, and, if so, what type it was. He will want to know the form in which it was administered, the container in which it was kept, how much was taken and how much was left.¹⁰⁴ The suicide (like many medical witnesses!) usually does not know the lethal dose of the poison used and will take an excessive amount. Death may occur before all of the poison is absorbed from the stomach. That poison which is left in the stomach could not have caused death, unless it was a corrosive poison, and yet time and again the medical examiner will believe that the cause of death has been proved by an analysis of the stomach contents alone without either a qualitative or quantitative analysis of the tissues. Many qualified pathologists are not competent toxicologists, so that in any case of suspected death from poisoning liberal quantities of all body fluids and tissues should be preserved for expert toxicological examination.¹⁰⁵

The suicide may dilute a corrosive poison or use other methods to mix and administer it, thus indicating his intent. If he obtained it under pretext, that raises a suspicion of suicide.

¹⁰³ For instance, in *Allison v. Bankers Life Ins. Co.*, 230 Ia. 995, 299 N. W. 889 (1941), where deceased was found lying near the exhaust pipe of his car in a secluded woods, with his shirt in a position to suggest that it had been used as a hood, and with the ignition on and hand throttle pulled out, the court said: "If decedent had intended suicide by inhaling monoxide gas, it is unlikely he would have attempted it outdoors." But would the court have declared it suicidal had the death occurred in a garage? This speculation about what the court would have done had it been in the deceased's shoes may be found throughout judicial opinions. Thus, another court pointed out that the insured surely did not commit suicide with a rifle in a closet, because "a much more plausible appearance of accident could be simulated somewhere on the proposed fishing trip." *Gamer v. New York Life Insurance Co.* (C. C. A. 9, Mont.), 76 F. (2d) 543 (1935). So uncertain is the evidence in carbon monoxide deaths that although they are unquestionably among the leading methods of suicide, they are very infrequently contested in court proceedings in suits for insurance. Gunshot wounds, on the other hand, are subject to more scientific analysis, and therefore furnish twice as much litigation as all other methods combined.

¹⁰⁴ One of the best illustrations of the unreliable nature of lay testimony and the difficult problem confronting an appellate court is *Bock v. New York Life Insurance Co.* (unreported, Tenn.), 1 CCH Life Cases 21 (1938). A youth bought potassium cyanide on a pretext and, after taking some of it in his room, walked past his mother into the yard, fell and was supposed to have struck his head. There was no autopsy. The family doctor disagreed with another doctor as to the appearance of the body, the presence or absence of bruises and blood and the cause of death. The sister claimed that she found the bottle of poison in the yard still wrapped. The druggist who sold the poison weighed it and found that 60 grains were missing. The undertaker, a relative of the deceased, said that when he talked to the druggist, the latter was uncertain whether any of the poison had been removed. The jury returned a verdict for the beneficiary, but the court reversed the judgment.

¹⁰⁵ McNally; Walker, Joseph T.: Scientific evidence in poisoning cases, *Clinics*, 1943, i, 1520; Report on the Autopsy, an outline prepared by a Conference Group on Pathology of the National Research Council, Jr. Tech. Meth. and Bull. Internat. Assoc. Med. Mus. No. XXIII, pp. 65-70, 1943; Maldeis, Howard, J.: Post mortem examination in cases of suspected poisoning, *Am. Jr. Clin. Path.*, 1943, xiii, 165; Gettler, Alexander O.: The significance of some toxicologic procedures in the medicolegal autopsy, *Am. Jr. Clin. Path.*, 1943, xiii, 169; Jetter, Walter W. and McLean, Regina: Biochemical changes in body fluids after death, *Am. Jr. Clin. Path.*, 1943, xiii, 178.

(b) What was the deceased's mental and physical reaction to the poison?

The poison may be fairly easy to distinguish from harmless substances by size, shape, color, container, odor and taste. If the poison was caustic, the deceased must have known what was taken as soon as it touched the lips and tongue. Then why was it swallowed? Why was it not expelled? Why were there no burns on the chin or face? The deceased may have been drunk, drugged, or sleepy, or in some other condition explaining why the poison was taken. However, if the deceased discovered what he took before losing consciousness, then he most certainly would have sought aid or made some outcry of pain, unless suicide had been intended.¹⁰⁶

In many poisoning cases there will be much testimony and disagreement about the outward appearance of the deceased, the "look on his face," and the position of the limbs, all of which may or may not be considered by a jury as indicating accident or suicide or even death by some other means.

(c) Did the deceased know the deadly character of the poison taken and the quantity he took?

Idiosyncrasy¹⁰⁷ to a drug, medicine or poison may cause an "accidental result." So also where the deceased did not know either the proper medicinal dose or the lethal dose, it is conceivable that he took an "overdose" of some "medicine" with lethal or poisonous effect.¹⁰⁸ Alcohol or some other substance or condition of the body may have created a synergistic or enhanced effect of a non-lethal dose of "medicine" so that it became poisonous and resulted in death.¹⁰⁹ In almost every litigated case of death by poisoning some effort will be made to show that the deceased mistook the poison for some medicine of similar odor, taste, color, size, shape or container.

(d) What was the occasion for use of the poison?

In some cases there could have been no other occasion for the purchase, concealment and then ingestion of the poison except suicide. However, it may be shown that the poison was purchased and used as a medicine or sedative or to kill rats or to use in the deceased's trade. Poisons are found in almost every household, and, unfortunately, many are poorly marked or their proper use unknown.

C

HANGING

Suicide by hanging is common in males¹¹⁰ and death by hanging is such strong prima facie evidence of suicide that the mere proof of hanging should

¹⁰⁶ f. n. 68, supra.

¹⁰⁷ See: 152 A. L. R. 1286; Bauder, Reginald, I.: Sulfa Drug Poisoning as an Accident, Proc. Ins. Law Sec., Amer. Bar. Assoc., p. 152 (1944).

¹⁰⁸ Would the death be accidental or caused by "accidental means?" See 111 A. L. R. 1286, and annotations cited.

¹⁰⁹ Walker, J. T., op. cit. supra, f. n. 105, p. 1534; Jetter, W. W. and McLean, R.: Synergistic effect of phenobarbital and ethyl alcohol, Arch. Path., 1943, xxxvi, 112; Dille, J. M., and Ahlquist, R. P.: Synergism of alcohol and sodium pentobarbital, Jr. Pharm. and Exper. Therap., 1937, lxi, 385.

¹¹⁰ Taylor, p. 427; Glaister, p. 218: Four-fifths of such suicides are males. Taylor, p. 427, and see reports in f. n. 100, supra.

overcome the presumption against suicide, dispense with proof of motive and cast the burden of going forward with the evidence upon the party claiming that death was accidental.¹¹¹ Accidental hangings are rare, but may occur as a result of "experiments," usually involving youths.¹¹² If there has been a fall, accidentally resulting in hanging, attendant bruises and other circumstances may show the absence of suicidal motive or mechanism. The medical witness will not be able to show from a mere examination of the body that the death was accidental rather than suicidal,¹¹³ but he may be able to show that it was homicidal, not suicidal, or that the body was strung up either during life or shortly thereafter to conceal the crime.¹¹⁴ There are numerous cases reported in which persons have hanged themselves in a sitting or even lying position.¹¹⁵ If the body is completely suspended, there should be a chair or other object nearby to explain self-suspension, otherwise homicide is indicated.¹¹⁶

D

MISCELLANEOUS CAUSES

Blunt Impact. Of the thousands of deaths that occur each year as a result of motor vehicle and train collisions, there are comparatively few due to suicide,¹¹⁷ for the two reasons which commonly determine the choice of method: (1) the result is not certain, and (2) pain and disability may precede death. It is difficult to distinguish between suicide and accident in this class of cases, and the medical witness can be of no assistance¹¹⁸ except in finding disease which may have caused an accident. However, eyewitnesses may be able sufficiently to show that the death was deliberate,¹¹⁹ and other sources of circumstantial evidence mentioned elsewhere in the paper may make the finding conclusive. It is strange that the law, which permits a finding of willful and wanton misconduct on the part of a motorist, is reluctant to reach a similar result where the intent to destroy is directed against one's self.

¹¹¹ Webster v. New York Life Ins. Co., 160 La. 854, 107 So. 599 (1926); Taylor, p. 428; Moritz, p. 164; Smith, p. 256; Webster, p. 95.

¹¹² Taylor, p. 427; Draper, p. 288; Kerr, p. 137; Gonzales, pp. 261-262; Snyder, p. 141.

¹¹³ Witthaus & Becker, vol. 2, p. 241; Taylor, p. 427; Herzog, p. 224; Draper, p. 288; Gonzales, p. 262.

¹¹⁴ Smith, p. 257; Moritz, pp. 166-167; Snyder, p. 143.

¹¹⁵ Snyder, p. 142; Smith, p. 256; Gonzales, p. 261; Taylor, p. 430; Draper, p. 288; Witthaus & Becker, vol. 2, p. 281.

¹¹⁶ Smith, p. 256.

¹¹⁷ In the City of New York in 1941, there were 1059 suicides of which only 23 resulted from a jump in front of an auto or train. In the same year there were 607 pedestrian highway and train deaths due to accident. See f. n. 100, supra. Neither juries nor courts are willing to find suicide in this class of cases, and a successful defense on that theory is rare.

¹¹⁸ Kerr, p. 105; Webster, p. 151, and pp. 157-158; Herzog, p. 286; Gonzales, p. 108; Smith, p. 124 and p. 133; Taylor, p. 266; Snyder, pp. 77-78; Glaister, p. 381 and p. 389; Witthaus & Becker, vol. 2, pp. 94-95; Draper, p. 378.

¹¹⁹ In International Life Insurance Co. v. Carroll (C. C. A. 6, Tenn.), 17 F. (2d) 42 (1927), a federal judge, hopelessly in debt, involved in speculations which wrecked a bank and, called upon to resign by the bar association pending grand jury investigation, which resulted in indictments, ran his car off the road and straight into a ditch. The court held that there was substantial evidence of an accident.

Fall or Jump. The "fall or jump" verdict of coroners' inquests became common in the depression of the early '30's. There is little medical evidence which can be adduced to distinguish between the accidental fall and the suicidal jump, beyond showing, perhaps, physical and mental disorders or impairments which could account for the injury.¹²⁰

However, much circumstantial evidence may be marshalled to help the jury. It should be shown whether the deceased knew of the imminence of danger, whether the hall was dark when he fell down the elevator shaft, etc. There may or may not have been an occasion for the deceased to be in the window, on the balcony or roof or other place from which he fell. He may have been looking down at his wife who had just fallen from the window,¹²¹ or he may have been trying to get a better view of the harbor,¹²² or he may have been just casually sitting in the window waiting to sign over his home, insurance and other property to escape a prosecution for embezzlement.¹²³

The condition of the shade, window and screen before and after the fall may show that they were all deliberately raised and not accidentally pushed open. Marks on the ledge may show that the deceased climbed into the window. Measurements and photographs should be made of the place from which deceased fell, the relative location of all objects (such as radiators and chairs) in the room to show whether the deceased could or could not have accidentally fallen or whether he deliberately climbed into the opening. The suicide will often sit on a ledge for quite a time before summoning enough courage to jump. Therefore, there are usually more eyewitnesses to suicidal jumps than to other methods of self-destruction.¹²⁴ Moreover, they are commonly accomplished in public places, and in some cases with apparent utter disregard of the safety of others.

Examination of the body by the medical witness will not show anything to differentiate a jump from a fall, unless the height was not great, and in such cases it is of slight importance to show the parts of the body which received the first impact.

There is one type of expert evidence to which resort is frequently made. Measurements of the distance of the vertical fall, the distance of the impact from the place of fall, and the weight of the body may be used in computing whether the deceased either fell or jumped. In one case the deceased who had been sick in a hospital, was depressed and had threatened his life, was found 14 feet from the wall of the hospital under his window which was

¹²⁰ A discouraging example of poor reasoning is that of *Smith v. Durham Life Insurance Co.*, 202 S. C. 392, 25 S. E. (2d) 247 (1943). The deceased fell or jumped from the fifth-floor window of a hospital. The back of his head was "bashed in" by the fall. This was part of the evidence from which it was inferred that he fell and did not jump!

¹²¹ The unusual, stranger-than-fiction case of *Lincoln Pet. Co. v. New York Life Ins. Co.* (C. C. A. 7, Ill.), 115 F. (2d) 73 (1940), partially reviewed in f. n. 57, *supra*.

¹²² *Connecticut General Life Insurance Co. v. Maher* (C. C. A. 9, Colo.), 70 F. (2d) 441 (1934).

¹²³ *Oubre v. Mutual Life Insurance Co. of N. Y.* (La. A.) 21 So. (2d) 191 (1945).

¹²⁴ Even an eyewitness will not be able, in some cases, to make the distinction between accident and suicide. Compare majority and dissenting opinions in *Lincoln Pet. Co. v. New York Life Insurance Co.* (C. C. A. 7, Ill.), 115 F. (2d) 73 (1940).

30 feet from the ground. A professor of mathematics testified that the body must have been travelling at about 30 miles an hour (about 45 feet a second) when it hit the ground; that under such circumstances it would not bounce; and that considering the measurements given the position of the body indicated an expenditure of horizontal energy at the window level which would be equal to a 4 foot 4 inch standing broadjump.¹²⁵ In another case a physicist computed the horizontal velocity of the body at the window level to be 11 feet per second, equivalent to a trotting run, and said that if the deceased had fallen, rather than jumped from the window 40 feet from the ground, he would have been found only 2 or 3 feet from the wall instead of the actual distance of 17 feet.¹²⁶

Drowning. It is usually impossible for the medical witness to determine whether a death by drowning is accidental, suicidal or homicidal in absence of marks on the body indicating injury before immersion in water.¹²⁷ It is often difficult to be certain that death resulted from drowning, especially where the body is recovered days later and has undergone putrefaction or has been damaged by marine life or ship propellers in such a way as to confuse the determination of the cause of such changes and wounds.¹²⁸ The medical examiner will be called upon to state how long the body was in the water, whether death occurred before or after immersion, whether certain marks or physical changes occurred before or after entry into water. The answers to these questions may or may not help in determining the circumstances attending the immersion and death. Here again disease, alcoholism and other facts which may be disclosed to the medical examiner or by investigation will assist in determining the cause of drowning.¹²⁹

Did the deceased know of the dangers involved, the depth of the water, the swiftness of the current, the presence of tidal currents or the whirlpool, etc.? What occasion did he have to be near or in the water? Was he on a fishing trip or gathering driftwood? Could he swim? Was the bank steep and the ledge slippery? Was the breath apparently knocked out of him when he became sleepy and fell off the bridge as he was sitting on the rail, and did he struggle with death for a moment before he was pulled under?¹³⁰

In a recent case the deceased was shown to have been in a desperate financial condition, and his relations with his wife were strained. After gambling all night he returned home at 5:00 a.m. His son unchained the door, but neither his son nor wife would speak to him, so he left the house. That afternoon he was found face down, drowned in a lily pond or fish pool

¹²⁵ *Hill v. New York Life Insurance Co.*, 322 Ill. A. 690, 54 N. E. (2d) 88 (1944), s. c. 307 Ill. A. 381 N. E. (2d) 183 (1940).

¹²⁶ *Christensen v. New England Mutual Life Insurance Co.*, 71 Ga. A. 393, 31 S. E. (2d) 214 (1944), s. c. 197 Ga. A. 807, 30 S. E. (2d) 471 (1943), s. c. (unreported, Ga. A.), 9 CCH Life Cases 268.

¹²⁷ Witthaus & Becker, vol. 2, p. 329; Draper, pp. 268-269; Taylor, p. 414; Smith, p. 274; Gonzales, p. 286; Webster, pp. 101-102; Glaister, p. 194; Kerr, p. 130.

¹²⁸ Moritz, p. 170; Draper, pp. 261 and 270; Gonzales, pp. 282-286; Witthaus & Becker, vol. 2, pp. 326-332; Smith, p. 269; Taylor, pp. 409-410; Snyder, p. 156.

¹²⁹ Gonzales, p. 279; Smith, p. 274; Taylor, p. 415; Draper, p. 268; Snyder, p. 157.

¹³⁰ *Hall v. Progressive Life Ins. Co.*, 61 Ga. A. 792, 7 S. E. (2d) 606 (1940).

in back of his home. It was 7 feet long, 5 feet wide and 2 feet deep, and, with the body in it, the water was about 16 inches deep. The steps leading to the pool were unstable and loose; an almost empty whiskey bottle was nearby; there were several deep, long cuts on the deceased's head, one of which a doctor said "was of itself sufficient to cause unconsciousness"; and "what appeared to be blood" was in the pool. It was the theory of the wife, beneficiary under policies providing accidental death benefits for which suit was brought, that her husband went to the fish pool to repair a leak in the bottom or to rearrange the cattails about the location of which he had argued with his wife a few days before; that he had been drinking and lost his balance when the step turned, causing him to fall, strike his head, become unconscious and drown. The jury evidently believed this theory and returned a verdict for the widow. The court on appeal reversed the judgment and ordered judgment for the defendant.¹³¹

Strangulation, Suffocation, Smothering, Choking, and Asphyxia (other than by Hanging, Drowning and Poisoning). It is rare to find either accidental or suicidal deaths by any of these methods.¹³² Most strangulations are homicidal. Attendant circumstances, other than those furnished by the medical jurist, will be of greatest importance.¹³³ Infancy, alcoholism, drugs, imbecility, epilepsy, and various other diseases, are factors in accidental deaths within this group.¹³⁴ Cases of the accidental lodgment of food or other articles in the throat, trachea, or lungs, causing death by obstructive asphyxia, are reported from time to time.¹³⁵ Strangulation by one's own

¹³¹ We have omitted one important bit of evidence to show how strong circumstantial evidence may be and yet be misleading. A long suicide note was found at 8:30 a.m., showing the motive (domestic trouble) and advising his wife: "You'd better destroy this note, for anything that happens to me must be an accident. Remember that! It'll make a lot of difference in your insurance. That ought to keep you quiet for money means more to you than anything else, and the knowledge of this note would mean that you would collect about \$5,000 less insurance. \$5,000 ought to keep your mouth shut, but it's up to you." The wife at first wanted to destroy the note unread; her son prevailed upon her to read it; she did and tore it up, being unable to find a match to burn it, and threw it into a garbage sack. Later she turned over the pieces to the coroner. At trial she testified that her husband had written a "scare note" before, but the court found that her testimony was "uncertain and unsatisfactory." The note found was written two days before death and after a quarrel, during which his wife belittled him in front of others, and, according to her testimony, she had followed him "clear out to the street" to get him "out of the mood he was in." *Home Life Ins. Co. v. Moon* (C. C. A. 4, W. Va.), 110 F. (2d) 184 (1940). Compare: *Bertschinger v. New York Life Ins. Co.*, 166 Ore. 307, 111 P. (2d) 1016 (1941), where a naturopathic physician guilty of one illegal abortion and on parole told his lawyer he would jump in the river before he would go through another case in court like that. Eight days later he killed a girl by the same method and was told it would be a coroner's case. Two days later he was drowned. A verdict for plaintiff was affirmed. Clearer thinking is found in *Koycheff v. Mutual Ben. H. & Acc. Assoc.*, 305 Mich. 660, 9 N. W. (2d) 883 (1943), and *Equitable Life Assur. Soc. v. Irelan* (C. C. A. 9 Mont.), 123 F. (2d) 462 (1941), both being cases of drowning.

¹³² In New York City in 1941, out of a total of 5,555 violent deaths investigated, there were only 63 deaths from asphyxiation other than hanging, drowning or poisoning. Statistical Report of the Chief Medical Examiner of New York City, 1941, p. 14; Smith, p. 261; Draper, p. 306; Witthaus & Becker, vol. 2, p. 241; Taylor, p. 440; Gonzales, p. 276.

¹³³ Taylor, p. 445, comments that "without circumstantial evidence the best medical opinion in these cases (of strangulation) will often amount to nothing."

¹³⁴ Moritz, p. 162; Smith, p. 263; Gonzales, p. 274.

¹³⁵ 21 of the 63 deaths resulting from obstructive asphyxiation in New York City in 1941 were from this means. f. n. 132, supra.

hands or by ligature using a tourniquet device is possible, although medical experts may be found with a contrary opinion.¹⁸⁶ There are a few cases reporting death by the voluntary blockage of the air passages with all manner of missiles, with self-destructive intent, but such persons are usually mentally defective. Electrocution may cause death by respiratory failure or ventricular fibrillation. Several suicides by this method have been reported but accidents are much more common.¹⁸⁷

One case well illustrates the uncertainty of much evidence introduced in all cases where the problem of accident or suicide must be solved. A man earning \$18,000 a year but over \$1,000,000 in debt but with no other apparent motive for suicide is said to have contracted neuralgia in his head from a heavy fog. He used an electric heating pad and obtained relief. He was found dead in his room with the cord from the pad in a noose around his neck, and the other end of the cord tied to the wires of an incomplete electric fixture. There was some dispute about the position of his body, the tightness of the cord and whether, as he lay against the wall, the cord was taut. Three physicians who performed an autopsy described a typical hanging bruise running around the neck, a small bruise on the side of the neck, and no evidence of an electric burn. One embalmer said that one mark "seemed like a burned place similar to an electric burn," and the other embalmer said the mark "appeared to be a burn and was brown and parched looking." An electrical expert showed how it was "possible" for a current to pass through the wires and into the body and said that fine wires in the knot were beaded "as though an arc had jumped across which would probably have caused a shock." He also said that 120 to 130 volts were "not supposed" to be enough to kill a man, but that there was uncertainty about it; that some persons were more susceptible to shock than others and that certain parts of the body were more sensitive than others.

The beneficiary first advanced the theory of murder, but this the court rejected for the reason that there was no evidence to support it.

The beneficiary then showed that a few weeks before her husband's death a friend of his was found dead from what appeared to be self-strangulation with a shoestring; that her husband had doubted this as possible and on one occasion undertook to demonstrate with his necktie that this was not possible; that her husband was of "an experimental turn of mind" and must have been attempting to demonstrate that his friend had not committed suicide; and that he probably electrocuted himself accidentally. The court said that this was pure conjecture; that "it is inconceivable that deceased would conduct, in solitude, a pointless experiment of so dangerous a nature"; that "reasonable men do not so recklessly trifle with death"; that whether the deceased died of strangulation, electrocution or both, he was killed as he had pre-arranged; and that the lower court had properly directed a verdict

¹⁸⁶ Kerr states that "suicide by this means is out of the question," p. 138. Compare Gonzales, p. 272; Taylor, p. 440; Witthaus & Becker, vol. 2, p. 241; Smith, p. 260.

¹⁸⁷ Snyder, p. 227; Smith, p. 241; Gonzales, p. 296.

for the defendant. It may also be mentioned that eleven months after the death the coroner held an inquest at which the jury found that the death resulted from "external violence or homicide." The record of the inquest was properly excluded from evidence.¹³⁸

Cutting. It is not uncommon that a person will die of accidentally inflicted incised wounds of the neck or wrists, but in virtually all of such cases the surrounding circumstances will clearly point to the cause of the wounds.¹³⁹ The difficulty does not lie in reaching a choice between accident and suicide, but rather in determining whether the wound was suicidal or homicidal.

Suicidal wounds of the neck are usually found above the thyroid cartilage on the left side in right-handed persons and on the right side in left-handed persons.¹⁴⁰ They may be either deep or superficial, regular or irregular, but are usually deep, ragged and slanting diagonally with the deepest cut at the beginning of the stroke.¹⁴¹ Multiple strokes of the instrument may be found in one wound.¹⁴² Most characteristic of all are several superficial cuts at the beginning of the wound, the so-called "hesitation" marks of the suicide.¹⁴³

An interesting case is that in which a man was found bleeding profusely from a deep cut of his right wrist, a long blood-stained knife nearby. The medical examiner and another physician testified that the wound was self-inflicted because of the presence of "hesitation" marks. No other physician testified. Yet the court held that other evidence made the case one for the jury rather than for the court to determine.¹⁴⁴

Stabbing. Where a stab wound is made with a knife or other hand-wielded weapon in a suicide, it is usually found in or near the region over the heart, although it may rarely appear elsewhere, and is directed from right to left in a right-handed person and from above downward.¹⁴⁵ Several stab wounds in a circumscribed area indicate suicide rather than homicide, and almost completely exclude accident.¹⁴⁶ Since the *felo-de-se* may stab himself

¹³⁸ American National Bank v. Continental Cas. Co. (C. C. A. 6, Tenn.), 70 F. (2d) 97 (1934).

¹³⁹ Webster, p. 151; Gonzales, p. 210; Glaister, p. 359; Moritz, p. 38; Taylor, pp. 267-269; Snyder, p. 123; Witthaus & Becker, vol. 2, pp. 80 and 94; Kerr, pp. 94-96 and pp. 103-104; Smith, pp. 124, 128-129; Draper, p. 380.

¹⁴⁰ Moritz, p. 38; Taylor, p. 268; Witthaus & Becker, vol. 2, p. 78; Snyder, p. 127; Smith, pp. 128-129; Gonzales, pp. 211-212.

¹⁴¹ Kerr, pp. 103-104; Moritz, p. 38; Smith, p. 128.

¹⁴² Kerr, pp. 103-104.

¹⁴³ Gonzales, p. 211; Moritz, p. 38; Smith, p. 129; Snyder, p. 127.

¹⁴⁴ Facts purposely omitted, and this time showing the importance of circumstantial evidence (compare *f. n.* 131, *supra*), are that the deceased, who apparently had no motive for suicide, was in the grinding and cutlery business and was found at his shop where he had been buffing large knives on a rag buffing wheel with a speed of 1400 r.p.m.; that the wheel was wobbly and had a deep cut in it; that there were blood stains on the ceiling above and the floor below the wheel; that the knife found had been partially buffed; that the deceased had made plans to go to a show with his wife later in the afternoon; that when his wife arrived at the shop he sought her help. One confusing fact, never explained, was why the deceased did not rush away from the machine and seek aid instead, possibly, of lying down by his machine until he was found. *Kirschbaum v. Metropolitan Life Insurance Co.*, 133 N. J. L. 5, 42 A. (2d) 257 (1945).

¹⁴⁵ Gonzales, p. 207; Smith, p. 129; Draper, p. 380; Witthaus & Becker, vol. 2, pp. 73, 75.

¹⁴⁶ Gonzales, p. 208.

more than once through a single opening and since multiple stabbings indicate suicide, the examiner should carefully determine the course and number of all wounds inside the body. Rarely a butcher or cook may run a knife into the abdomen by accident while drawing it toward himself.¹⁴⁷ Falls and other accidents may cause an impaling of the body on some object, or flying splinters or glass may cause fatal stab wounds.¹⁴⁸ In such cases, and in homicide, the pattern—multiple but general—and direction will usually show that there was no suicide. Surrounding circumstances are important.

A man and his wife were in the kitchen and he was wiping the dishes. As he was wiping a paring knife she heard him say, "Here goes." She looked at him and saw blood on his shirt. He laid down the knife, took a few steps and died shortly thereafter. A knife wound two inches deep had penetrated the heart. He had had business reverses, had threatened self-destruction and had been drinking. His wife, the beneficiary of an accident insurance policy, introduced evidence that he was in good health and spirits, in fair financial condition, had no domestic trouble, was temperate and jovial and liked to play with children, was given to mock heroics and "play acting" and frequently moved a knife toward his body, exclaiming, "Here goes," and then turning the knife just before striking his body with his fist, for the purpose of frightening others with this performance which he called the "Dutch act." The court, in affirming a judgment for the beneficiary, held that there was substantial evidence that he accidentally killed himself.¹⁴⁹

Burning. Suicide by this method is rare.¹⁵⁰ It may be used for homicide or for concealment of a homicide or suicide by other methods.¹⁵¹ Death by burning is almost always accidental.¹⁵² Disease may be a direct or indirect cause of the fire and thus possibly affect a recovery for accidental death benefits, but the same rule applies to almost all other apparently violent deaths and is beyond the scope of this paper. A careful consideration of all of the attendant circumstances together with such general inquiries suggested elsewhere in this paper will usually disclose whether the death was accidental or suicidal.¹⁵³ Of chief importance will be a search for any marks of violence which may have indicated accident, suicide or homicide preceding the death by burning.

In a recent case the deceased was suffering with rectal cancer and was confined to his room under opiates. He had day and night nurses; the night nurse went off duty at 7 a.m. and the day nurse came on duty at 8 a.m. His wife usually cared for him between 7 and 8 a.m. but on the day of his death left at 7 a.m. with the night nurse to whom the insured had made veiled threats of suicide. When the day nurse arrived at 8 a.m. she found the bed-

¹⁴⁷ Ibid.

¹⁴⁸ Gonzales, p. 208; Snyder, p. 126; Smith, p. 128.

¹⁴⁹ Missouri State Life Insurance Co. v. Pater (C. C. A. 7, Ind.), 15 F. (2d) 737 (1926).

¹⁵⁰ Glaister, p. 257; Smith, p. 237; Webster, p. 116; Gonzales, p. 292.

¹⁵¹ Smith, p. 236; Snyder, p. 170; Gonzales, p. 292.

¹⁵² Glaister, p. 257; Taylor, p. 394; Kerr, p. 109; Smith, p. 236; Webster, p. 116.

¹⁵³ Smith, pp. 237-238; Taylor, p. 394; Kerr, p. 109; Webster, p. 116.

room on fire and the doors, which had been unlocked at 7 a.m., locked. The shades, which had been up when the night nurse left, were pulled down. The deceased was found dead with the lower part of his body burned and the odor of inflammable rubbing alcohol on the body, the empty bottle in a basket. There was some dispute whether a gas heater was near to or distant from his bed. It was plaintiff's theory that papers had fallen off the bed and ignited it and that the deceased was unable to help himself in time. A doctor said that with opiates given to the deceased he would not have much feeling in his body. A jury returned a verdict for the defendant, but the lower court granted a new trial on the ground that there was insufficient evidence to support a verdict of suicide. On appeal the conclusion was affirmed by the California Court of appeals. However, the California Supreme Court held that there was sufficient evidence to support a verdict either of accident or suicide but that it had no power to interfere with the trial court's conclusion that the case should be retried.¹⁵⁴

VI

CONCLUSIONS AND SUMMARY

1. The problem of determining whether a death was accidental or suicidal frequently arises and is of great importance in coroners' investigations, insurance claims and workmen's compensation proceedings. This determination infrequently becomes necessary in several other fields of law.

2. In cases arising in insurance law and under workmen's compensation statutes, procedural rules relating to the burden of proof, presumptions, and the admissibility and sufficiency of evidence substantially affect the final result and in many cases seem as important as real evidence. Strange and unjust decisions of juries and courts have been due to several misconceptions which should no longer be followed: (1) the continued recognition of the presumption against suicide without any effort to reexamine it from a scientific viewpoint to determine its present-day validity; (2) the application of this presumption in cases where it is obvious that the deceased did not love life or fear death enough to deter him from suicide; (3) the application of this presumption to various types of violent deaths which are statistically proved to be more commonly suicidal than accidental; (4) the adherence to obfuscated rules of evidence and the treatment of the presumption against suicide either as evidence or as a rule of law upon which the court may instruct the jury or as a "fact of life" which the jury may consider along with other evidence in finding that a death was accidental; (5) the failure to distinguish between suits on life policies where the burden of proving suicide is on the defendant, and suits for accidental death benefits where the burden of proving accident is on the plaintiff and no burden of proving suicide is on the insurer; (6) the departure of courts from rules of law universally applied

¹⁵⁴ *Brooks v. Metropolitan Life Insurance Co.* (Cal.), 163 P. (2d) 689 (1945), s. c. (Cal. A.), 159 P. (2d) 424 (1945).

in all other cases, notably those rules requiring the production of substantial evidence sufficient to remove an issue from the realm of mere guess and speculation.¹⁵⁵

3. Other factors contributing to unjust results where the accident-or-suicide problem arises are: (1) lack of proper medical, police and other investigation at the scene and time of the injury; (2) failure to pursue all available avenues of investigation indicated at the time; (3) failure to obtain and preserve the evidence in a form in which it may be used without contradiction later on; (4) the free employment of unqualified "experts" to testify about things they do not know but in a way for which their price was paid; (5) incompetence of jurors to decide scientific controversies; (6) prejudice against insurance companies and employers and in favor of injured persons and widows; (7) all of the other unsavory results of ignorance and dishonesty, both in and out of court by lay and expert witnesses.

4. Proof that a death was accidental or suicidal may be made by resort to either direct or circumstantial evidence, and in general this evidence may be described as External or Internal. External Evidence is directed to the physical facts and circumstances surrounding the death from which one may conclude whether the injury was self-inflicted. Internal Evidence is designed to prove whether this self-inflicted injury was intentional, and may be drawn from facts and events preceding, attending or following the injury.

5. Medical jurists have laid down numerous general rules of little assistance in reaching a conclusion in any one particular case in which a death may have been either accidental or suicidal.

6. Specific problems related to various kinds of violent deaths have been examined. Except in the case of gunshot wounds, the medical witness will seldom be able to express an opinion, from an examination of the body alone, whether death was accidental or suicidal. After the physical cause of death is once established, the ultimate decision of whether a death was caused by accident or suicide will depend almost wholly upon non-expert evidence, excepting again a death by gunshot wounds. In this one class of cases, the medical witness with a fundamental knowledge of firearms and reasonably accurate information concerning the weapon and cartridge used can furnish invaluable evidence of the relative position of the gun to the deceased at the time it was fired.

ADDITIONAL REFERENCES

1. APPLEMAN, J. A.: Insurance Law and Practice, 1941, West Publishing Co., St. Paul.
2. BECK, T. R., and BECK, J. B.: Elements of Medical Jurisprudence, 1835, ed. 5, Steele, Skinner, Little & Gould, Albany.
3. COOLEY, R. W.: Briefs on the Law of Insurance, ed. 2, 1928, Vernon Law Book Co., Kansas City.
4. CORNELIUS, M. P.: Accidental Means, 1932, R. M. Chandor, Publisher, Indianapolis.

¹⁵⁵ In *Gorham v. Mutual Benefit Health & Acc. Assn.* (C. C. A. 4, N. C.), 114 F. (2d) 97 (1940), the court said: "A suicide case should be tried like any other case, and metaphysical reasoning about presumptions and burden of proof should not be permitted to obscure the real issue, as has been done in so many cases."

5. COUCH, G. J.: *Cyclopedia of Insurance Law*, 1931, The Lawyers Cooperative Publishing Co., Rochester.
6. DRAPER, F. W.: *Textbook of Legal Medicine*, 1910, W. B. Saunders Co., Philadelphia.
7. GLAISTER, J., SR., and GLAISTER, J., JR.: *Medical Jurisprudence and Toxicology*, ed. 5, 1931, William Wood & Co., New York.
8. GONZALES, T., VANCE, M., and HELPERN, M.: *Legal Medicine and Toxicology*, 1937, D. Appleton-Century Co., New York.
9. HATCHER, J. S.: *Textbook of Firearms Investigation, Identification and Evidence*, 1935, Small Arms Publishing Co., Marines, North Carolina.
10. HERZOG, A. W.: *Medical Jurisprudence*, 1931, Bobbs-Merrill Co., Indianapolis.
11. JONES, B. W.: *Commentaries on the Law of Evidence*, ed. 2, 1926, Bancroft-Whitney Co., San Francisco.
12. JOYCE, J. A.: *The Law of Insurance*, ed. 2, 1918, The Lawyers Cooperative Publishing Co., Rochester.
13. KERR, D. A. J.: *Forensic Medicine*, 1935, A. & C. Black, Ltd., London.
14. McNALLY, W. D.: *Toxicology*, 1937, Industrial Medicine, Chicago.
15. MORITZ, A. R.: *The Pathology of Trauma*, 1942, Lea & Febiger Co., Philadelphia.
16. MORITZ, A. R., and DUTRA, F. R.: *Scientific evidence in cases of injury by gunfire*, *Arch. Path.*, 1944, xxvii, 340-349.
17. PHELPS, C.: *Traumatic Injuries of the Brain and Its Membranes*, 1897, D. Appleton Co., New York.
18. SMITH, S.: *Forensic Medicine*, ed. 5, 1943, J. & A. Churchill, Ltd., London.
19. SNYDER, L.: *Homicide Investigation*, 1944, Charles C. Thomas, Springfield.
20. STEWART, G. H.: *Legal Medicine*, 1910, Bobbs-Merrill Co., Indianapolis.
21. TAYLOR, A. S.: *Medical Jurisprudence*, ed. 12 (Amer.), 1897, edited by Clark Bell, Lea Brothers, New York.
22. VANDE GRIFT, W. B.: *Suicide and homicide by violence*, *Med. Clin. North Am.*, 1941, xxv, 423.
23. WALKER, J. T.: *Bullet holes and chemical residues in shooting cases*, *Jr. Crim. Law and Criminology*, 1940, xxxi, 497.
24. WEBSTER, R. H.: *Legal Medicine and Toxicology*, 1930, W. B. Saunders Co., Philadelphia.
25. WHARTON, F., and STILLÉ, M.: *Medical Jurisprudence*, ed. 3, 1873, Kay and Brother, Philadelphia.
26. WITTHAUS, R. A., and BECKER, T. C.: *Medical Jurisprudence, Forensic Medicine and Toxicology*, ed. 2, 1906, William Wood & Co., New York.

PENICILLIN IN THE TREATMENT OF PUTRID LUNG ABSCESS *

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DURING the last two decades our knowledge of the pathogenesis and pathological physiology of putrid lung abscesses has advanced remarkably. This inevitably led to great improvement in the quality of the surgical treatment of this serious disease so that an ever increasing number of such patients are now being treated effectively by surgical means.

At this time it is generally agreed that acute putrid lung abscesses which are accompanied by great toxicity or which show no rapid roentgenological improvement by medical measures, are best treated by early thoracotomy and pneumonostomy. This is also true of abscesses which progress, rupture into the pleural cavity, or give rise to persistent hemoptysis.

In fact there is an increasing number of physicians who believe that all acute putrid lung abscesses, regardless of their size or the severe toxic symptoms they engender, should be treated in this manner as soon as the diagnosis is made. This group has been encouraged in its beliefs by many writers, notably Neuhof and Touroff ¹ who in 1940 reported the operative results in 86 consecutive patients with acute putrid lung abscesses, 21 of whom had putrid empyema. Of these, 73 recovered, three died of septic complications post-operatively and four died of diseases other than the lung abscess. However, many other physicians have not been so fortunate in their results with surgical treatment of this serious disease. Sweet ² in 1940 reported a series of 125 cases of acute putrid lung abscess from the Massachusetts General Hospital. Of those operated on in this group 7.4 per cent died immediately post-operatively, 26.6 per cent died ultimately of the abscess or its complications, and only 43 per cent were cured. Sweet concluded that the results of the surgical treatment of lung abscess were on the whole disappointing. He stated that if there is a good chance of spontaneous recovery operation should be avoided, but if one can be reasonably certain that spontaneous recovery will not occur, then the sooner the operation is performed the better. This attitude echoes an earlier view of Cutler ³ who in 1936 stated that an intensive study of the case histories of the group he presented made it obvious that, if all such cases were submitted to operation, the mortality rate would be considerably cut down, but that in so doing we would submit to operation many patients who would have recovered spontaneously.

As a matter of fact spontaneous recovery occurs only in a small percentage of cases of acute pulmonary abscesses who seek hospital care. In

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From Medical Service of the Harlem Hospital, Dr. Oswald LaRotonda, Medical Director.

the Harlem Hospital in the past few years spontaneous recovery occurred in only eight, or 11 per cent, of 70 such patients. This recovery occurred only in patients who were not very toxic and had small abscesses, usually less than 3 cm. in diameter, with little perifocal pneumonia.

However, it is not the purpose of this discussion to reconcile these opposing views or to inject new material into the controversy, but rather to indicate that because of the views of Sweet, Cutler and others many acute putrid lung abscesses in private practice and in hospitals are observed for protracted periods of time in the hope that they will recover under medical treatment. During this period serious and often fatal complications frequently arise, such as septic embolism, progression of the abscess with the formation of multiple abscesses, fibrosis, atelectasis and bronchiectasis in the lung involved, extension into the opposite lung, and rupture into the pleura with putrid empyema. Moreover, while waiting acute abscesses become chronic abscesses and these rarely if ever recover spontaneously. Most distressing is the fact that patients with chronic abscesses are not cured with simple pneumonostomy, and the mortality rate is high, even with the best surgery, because of many grave complications.

There is therefore a great need for a method of treatment which would (1) increase the rate of recovery without surgical interference, (2) decrease the number and severity of pre- and post-operative complications and (3) make operative treatment generally safer and more effective.

When penicillin became freely available during the past year, we administered it to 13 patients with putrid lung abscess in order to explore its potentialities. Sulfadiazine was employed concurrently despite the fact that, when used by itself, it had no appreciable effect on a small series of patients so treated. It was hoped, however, that it might have a beneficial effect on the perifocal pneumonitis.

Although from 20 to 25 patients with acute putrid lung abscesses are admitted annually to Harlem Hospital, there were only 10 such cases in the hospital during 1944 and six during 1945. We are not certain whether this marked decrease in the last two years was fortuitous or due to the early and frequent use of penicillin in all kinds of pulmonary infection. As soon as the diagnosis of putrid lung abscess was definitely established and confirmed by roentgenograms the patient was given both sulfadiazine and penicillin. The sodium salt of penicillin was administered intramuscularly in doses of 25,000 units every three hours. The sulfadiazine was given in the usual manner, sufficient to establish and maintain adequate blood levels.

ACUTE PUTRID LUNG ABSCESS

Since October 1944 seven patients with acute putrid lung abscesses were admitted to the hospital. One of these recovered spontaneously before penicillin was used. The remaining six were treated with penicillin and sulfadiazine. These are presented in the order of their admission.

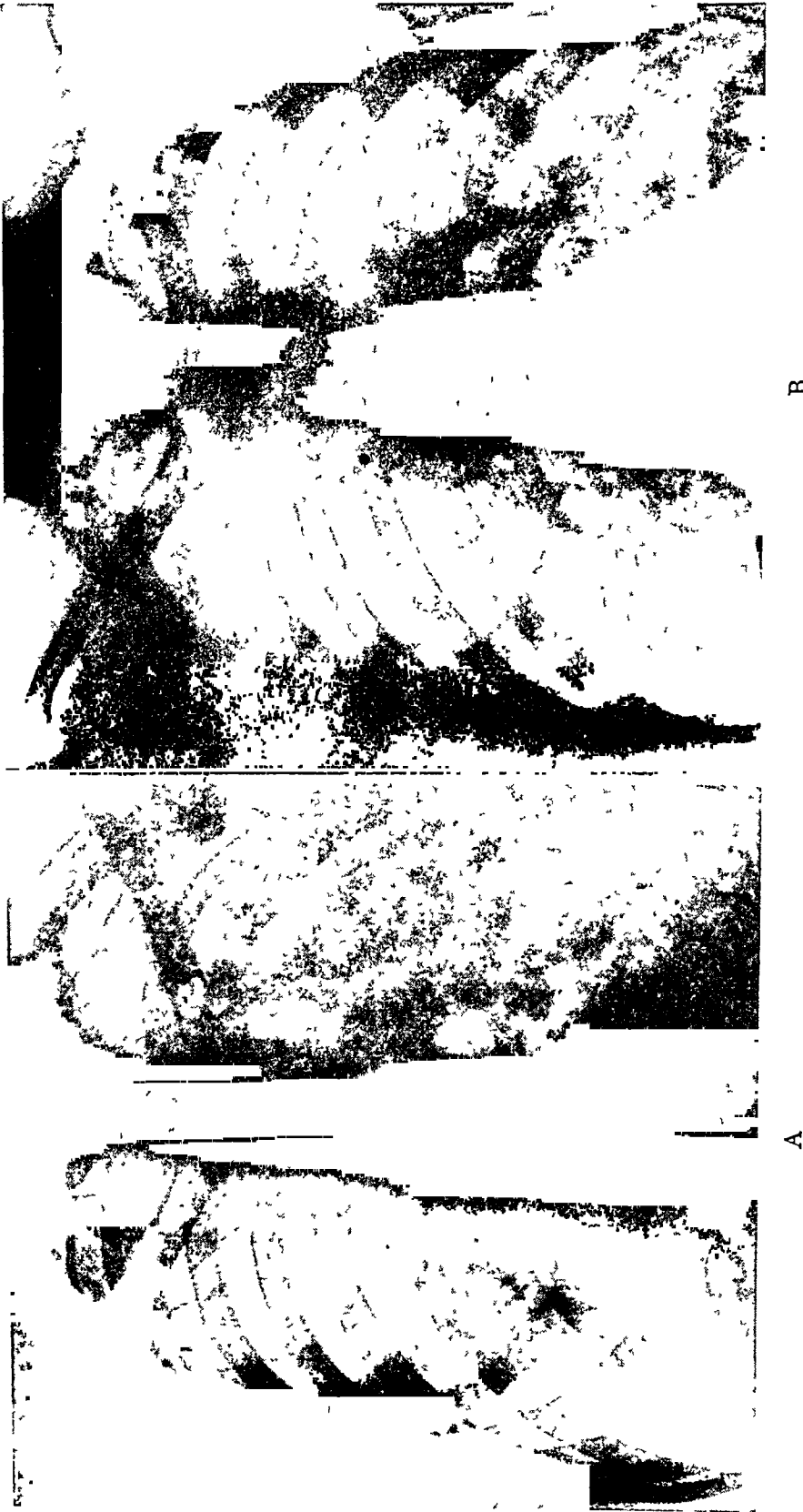
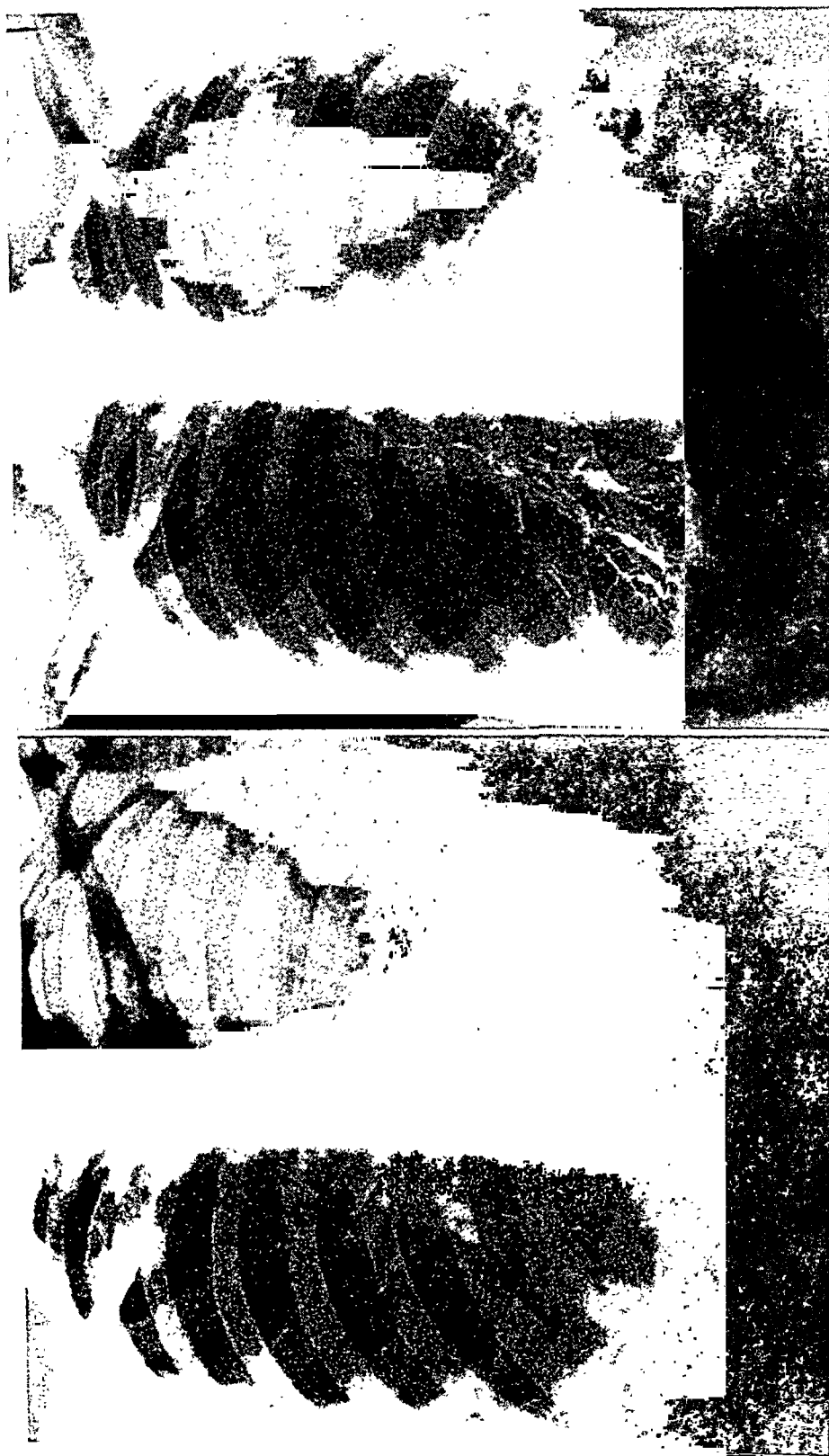


FIG. 1. Case 1, T. J. A. Film taken Oct. 24, 1944 showing diffuse infiltration and numerous cavities in the left lower lobe. B. Film taken Dec. 5, 1944 showing complete clearing of lesion.



A

B

FIG. 2. Case 2, I. R. A. Film taken April 24, 1945 showing diffuse infiltration with large cavity in the left lower lobe. Consolidation with cavity at right base. B. Taken June 21, 1945 shows bronchiectasis in left lower lobe.

CASE REPORTS

Case 1. T. J., a 49 year old male negro was admitted to Harlem Hospital on Oct. 21, 1944. He had suffered from frequent severe attacks of bronchial asthma since early youth. His temperature on admission was 102° F., pulse 120 and respirations 30 per minute. He appeared distressed and seriously ill. He expectorated large quantities of fetid sputum. The thorax was emphysematous in type. Expiratory wheezes were heard throughout both lung fields and scattered moist râles throughout both lower lobes. The admission roentgenogram of the chest revealed confluent consolidation of the entire left lower lobe with the moth-eaten appearance of early diffuse cavitation. A diagnosis of acute putrid lung abscess was made. On Oct. 22, 1944 penicillin and sulfadiazine therapy was started and this was continued to Dec. 5, 1944. He became afebrile and asymptomatic on Oct. 27. Serial chest films revealed continued clearing until Nov. 27 when the chest film was that of a normal lung. He was discharged on Dec. 8, 1944.

Comment. This patient was seriously ill with bronchial asthma and acute putrid lung abscess. He responded to the penicillin and sulfadiazine therapy with complete disappearance of the lung abscess.

Case 2. I. R., a desperately ill negress of 35 years, was admitted to Harlem Hospital on April 23, 1945. She gave no previous history of illness, operation or injury except cough for the preceding five weeks. Early in April she had a productive cough with blood streaked sputum. On April 16 she noted pain in the right lower chest. This became intense on the twenty-second, when she noted shortness of breath.

On admission her temperature was 103° F., pulse 120 and respirations 32 per minute. The breath was foul and the sputum was profuse and putrid. There were dullness and large moist râles over the lower two-thirds of the left lower lobe. The chest film on admission revealed a large abscess cavity in the left lower lobe with pneumonic involvement of this entire lobe and considerable pneumonia with small abscesses in the lower lobe of the contralateral lung. The sputum contained no acid-fast bacilli. On April 25 a surgical consultation for pneumonostomy was requested and treatment with sulfadiazine and penicillin was started preparatory to the proposed surgical intervention. This treatment was continued until June 15. Three days after the therapy was started she had improved markedly and her temperature fell to 101° F. On May 5 her temperature became normal; she remained asymptomatic and afebrile and obviously was no longer in need of surgical care. Serial roentgenograms revealed continued clearing of the abscess cavities and the pneumonic infiltration. On May 10 the abscesses were no longer visible. On June 21 a bronchogram revealed dilatation of the bronchi of the left lower lobe. She was discharged on June 25, 1945 and has been well and asymptomatic to the present time.

Comment. This patient had bilateral acute putrid lung abscesses with suppurative pneumonia in both lungs. The widespread putrid infection of the lungs cleared fully and promptly on sulfadiazine and penicillin therapy. She was left with a residual bronchiectasis in the left lower lobe. She was gravely ill and it is doubtful that she would have survived the operation which seemed necessary when she was admitted.

Case 3. L. McK., a 38 year old male negro, was admitted to Harlem Hospital on May 5, 1945. Throughout his life he had had frequent sore throats and nasal colds. He was well until April 22, 1945 when he began to cough and expectorate blood streaked sputum. His appetite was poor, he fatigued easily and lost 25 lbs. His



A

B

FIG. 3. Case 3, L. McK. A. Film taken May 14, 1945 showing large abscess with fluid level in upper portion of the right lower lobe. B. Film taken July 9, 1945 showing clear lung.

temperature was 104° F., pulse 124 and respirations 22 per minute. He was poorly nourished. The breath and sputum had a foul odor.

Physical examination revealed moist râles over the right infrascapular region. The chest film on admission revealed a huge cavity with a fluid level in the upper portion of the right lower lobe. The sputum contained no acid-fast bacilli. Penicillin and sulfadiazine were started the day after admission and by May 12 his temperature had fallen to 101° F. and the sputum was no longer foul. On May 21 he became asymptomatic and afebrile, and he remained well until his discharge. Serial chest roentgenograms revealed a clearing process in the left lung. The film of June 15 revealed no cavitation and the film of July 9 revealed a normal lung. He was discharged on July 12, 1945.

Comment. This patient had a large acute putrid lung abscess which cleared completely with penicillin and sulfadiazine. There were no pulmonary, pleural or metastatic complications.

Case 4. A. P., a 21 year old Puerto Rican male, was admitted to Harlem Hospital on July 19, 1945. He had been well until three days before admission when he had a chill and became feverish. He complained of pain in the right lower chest associated with nausea and vomiting. He coughed and expectorated foul sputum.

Physical examination revealed dullness and broncho-vesicular breathing over the right lower lobe posteriorly. The temperature was septic in type, fluctuating between 99° and 102° F. The pulse rate was 110 and the respirations 24 per minute. The chest film revealed a cavity with a fluid level in the lower third of the right lung field and below this there was a round area of radio-opacity which on the lateral film appeared to be due to an exudate in the oblique fissure. Treatment with penicillin and sulfadiazine was started on July 20, and continued until August 3, 1945. The sputum was repeatedly negative for acid-fast bacilli. Repeated aspirations of the chest failed to reveal the fluid noted on the roentgenograms. Because the patient's temperature had become normal and he was asymptomatic by July 22, further aspirations were not attempted. On Sept. 6 the cavity could no longer be visualized but in the last chest roentgenogram of Sept. 6, 1945 the radio-opacity in the right lower lobe was still present. He was ambulatory, afebrile and asymptomatic when he was discharged on Oct. 14, 1945.

Comment. This patient was believed to have had a ruptured putrid lung abscess and an interlobar empyema. Under penicillin and sulfadiazine therapy he became asymptomatic and the cavity disappeared but the interlobar shadow persisted. We have had no opportunity to follow his progress, but believe that he will need surgical care for the residual lesion.

Case 5. W. B., a 28 year old negress, was admitted to Harlem Hospital on July 20, 1945. She had had no previous illness, operation or injury. She complained of cough and expectoration of four weeks' duration. She felt weak and had lost 15 lbs. On July 20 she noted pain in the right lower chest which was aggravated by respiration and cough.

On admission her temperature was 102° F., pulse 90 and respirations 20 per minute. She coughed and expectorated foul sputum. The chest film revealed consolidation at the right lower lobe just lateral to the heart. Her Wassermann reaction was positive. Her sputum contained no acid-fast bacilli, but aerobic and anaerobic gamma streptococcus, *Staphylococcus albus* and *B. subtilis*. The temperature continued until July 25 when treatment with penicillin and sulfadiazine was started and continued until August 7, 1945. Her temperature became normal on July 28 and all



FIG. 4. *Case 5, W. B. A.* Film taken July 24, 1945 showing consolidation in the right lower lobe just lateral to heart.

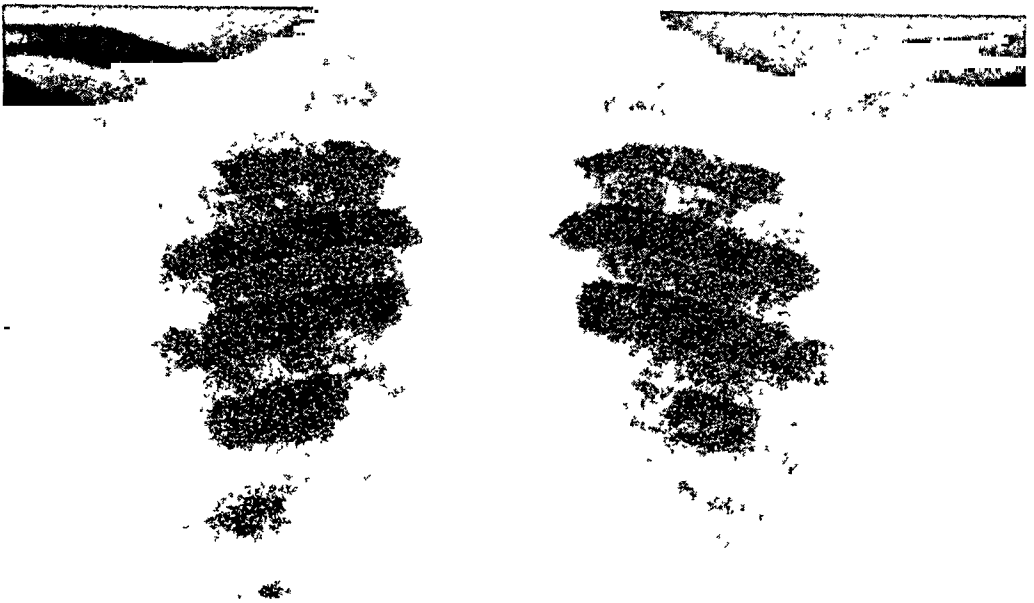
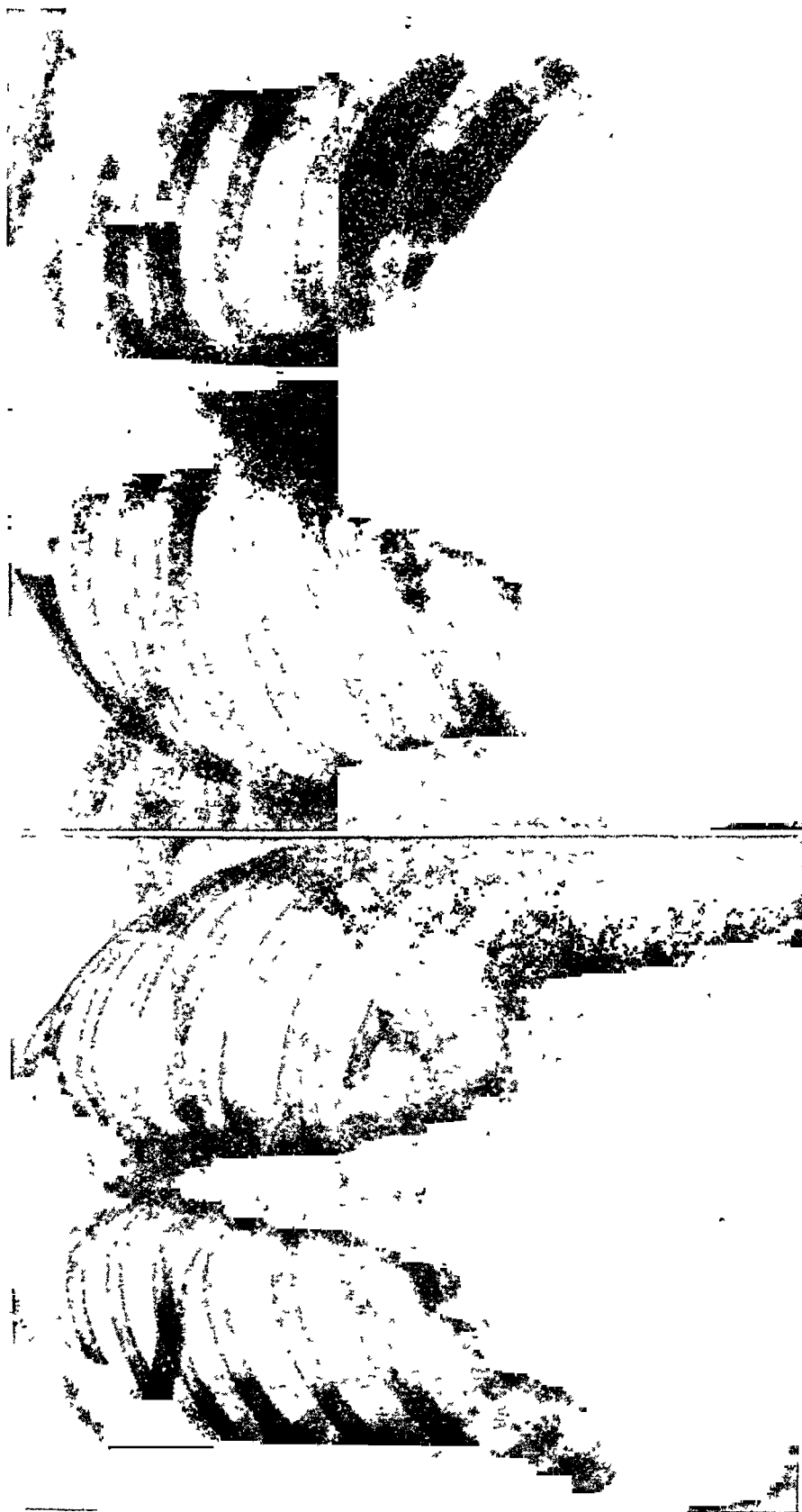


FIG. 4. *Case 5, W. B. B.* Film taken Aug. 20, 1945 showing clearing of lesion.



B

A

FIG. 5. Case 6, H. H. A. Film taken Oct. 29, 1945 showing consolidation in the right lower lobe with cavity and fluid level. B. Film taken Dec. 5, 1945 showing clearing of cavity and consolidation. There is some pleural thickening at right base.

symptoms had disappeared by July 30. On August 20 her chest roentgenogram revealed no abnormality. A bronchogram on August 22 failed to reveal any abnormality. She was discharged on August 25, 1945.

Comment. This patient had an early acute putrid lung abscess which healed promptly with penicillin and sulfadiazine therapy.

Case 6. H. H., a negress 37 years of age, was admitted to Harlem Hospital on Oct. 7, 1945. On Sept. 30, 1945 she had had a peritonsillar abscess incised. Two days later her temperature began to rise and her physician suggested hospitalization.

On admission her temperature was 105° F., pulse 120, respirations 24. Her teeth were carious. She had marked trismus of the jaw. The anterior pillar of the left tonsil was edematous and intensely red. The right anterior pillar had been incised and both tonsils were markedly enlarged. Small moist râles were heard over the right anterior chest.

On Oct. 14 the temperature again rose and reached 104° F. on Oct. 17. At this time flatness, diminished breath sounds and tenderness were elicited over the right lower lobe and a large radio-opaque patch was noted in the region of the right lower lobe on the chest film.

On October 29 the chest film showed a large cavity with a fluid level in the region of the right lower lobe. The septic temperature continued until Nov. 10, 1945 and she was then transferred to the chest service where a diagnosis of putrid lung abscess was made. With penicillin and sulfadiazine her temperature became normal on Nov. 15, 1945. On Nov. 29 the chest film no longer showed a cavity, but slight pleural thickening was present in the region of the previous radio-opacity.

Comment. This patient made a remarkable recovery from her fetid abscess of the lung. Whether or not it could have been prevented by a longer period of treatment with penicillin when she was first admitted, it is difficult to say. In the light of our present experience we would administer penicillin in such cases not only until toxic symptoms disappear but until the roentgenograms show complete clearing of the pulmonary process.

Summary. Six consecutive patients with acute putrid lung abscess were treated with penicillin and sulfadiazine. All became free from local and constitutional symptoms. They improved remarkably in weight and strength. In five there was complete recovery from the disease as judged from the chest roentgenograms. In one a previously noted encapsulated exudate remained symptom-free and unchanged. The almost moribund patient with multiple bilateral abscesses and widespread bilateral pneumonia made a remarkable recovery and was left with only slight asymptomatic bronchiectasis. Four of the patients were admitted with large abscesses and grave toxic symptoms and formerly would have fallen into the group requiring immediate surgical care. One would probably not have survived operative interference. On penicillin and sulfadiazine they made a complete recovery without operation. There were no complicating local or metastatic infections.

CHRONIC PUTRID LUNG ABSCESS

During the past year, seven patients with chronic putrid lung abscess were admitted to Harlem Hospital. One of these had formerly been oper-

ated on in another hospital. He came in with convulsions and died the same day of a ruptured brain abscess.

One had a large putrid right upper lobe abscess with a spillover to the lower lobe of about six months' duration. Another had had a large putrid abscess in the left lower lobe for about three months. The fourth developed a putrid lung abscess in the right lower lobe following operation for ruptured gastric ulcer a year prior to admission to the Harlem Hospital where a spillover to the left side was noted.

The fifth patient was seen about six months after she developed an abscess in the right lung following a right "pneumonic" process. The sixth patient had several large foul lung abscesses in the right lower lobe for six months prior to admission to our wards, and the seventh had a large foul abscess in the right upper lobe for at least eight months before he came under our observation.

In five of these the treatment with penicillin and sulfadiazine was followed by unmistakable improvement. There was remarkable amelioration of the toxic manifestations. Serial chest roentgenograms disclosed definite regression of the lesion in two and marked improvement in one. There were no septic or metastatic complications while under treatment and in our opinion all of them became better surgical risks after penicillin-sulfadiazine treatment than they were before the treatment was instituted. One patient died of ruptured lung abscess one month after the treatment with penicillin was discontinued.

DISCUSSION AND SUMMARY

In the past few decades there have been many reports of cures of isolated cases of acute putrid lung abscess with various chemicals, vaccines, and bacteriophage. Even artificial pneumothorax, obviously contraindicated in the treatment of such cases, came in for praise by some observers. The fact that the reported successes have not been reproduced with the respective methods of care in any fair group of patients with lung abscess suggests that the patients reported might have recovered spontaneously without treatment.

In the past year Roberts,⁴ Dawson and Hobby,⁵ Snook,⁶ and Smyth and Billingslea⁷ reported isolated cases of acute putrid abscess that recovered completely with penicillin therapy. The complete recovery of five of our six patients with such abscesses under the combined penicillin and sulfadiazine administration prompts the suggestion that this method of treatment deserves serious consideration and further extended trial, particularly since four of the patients belonged to a group heretofore considered in need of immediate surgical interference, one of whom would probably not have survived operation.

It is different in the case of chronic lung abscess. Here the lung and bronchi are converted by the reaction to the putrid infection into a maze of

fibrosis, multiple hard walled abscesses, bronchiectasis, atelectasis, and chronic pneumonitis, so that restitution to the normal can not be hoped for with medical care or even with extensive surgery. At times nothing short of lobectomy or pneumonectomy will save the life of the patient. Nevertheless the combined penicillin and sulfadiazine treatment in such cases is of inestimable value. It lessens toxicity, prevents further septic and metastatic foci, clears the surrounding pneumonitis, and improves the general condition of the patient so that he can better withstand the extensive operation indicated to bring relief.

It is important to bear in mind the need of continuing this combined penicillin sulfadiazine administration in acute putrid lung abscess not only until all toxic and local symptoms have disappeared but until the chest film shows no abnormal shadows in the segment of the lung involved. In chronic putrid abscess this method of care should be started preparatory to surgical intervention and continued after operation until all toxic symptoms disappear.

BIBLIOGRAPHY

1. NEUHOF, H., and TOUROFF, A. S. W.: Acute putrid abscess of lung: surgical treatments and results in 86 consecutive cases, *Jr. Thorac. Surg.*, 1940, ix, 439-449.
NEUHOF, H., TOUROFF, A. S. W., and AUFSES, A. H.: Surgical treatment by drainage of subacute and chronic putrid abscess of the lung, *Ann. Surg.*, 1941, cxiii, 209-220.
2. SWEET, R. H.: Lung abscess: analysis of Massachusetts General Hospital cases from 1933 through 1937, *Surg., Gynec., and Obst.*, 1940, lxx, 1011-1031.
3. CUTLER, E. C., and GROSS, R. E.: Non-tuberculous abscess of the lung, *Jr. Thorac. Surg.*, 1936, vi, 125-155.
4. ROBERTS, J. E. H., TUBBS, O. S., and BATES, M.: Pleural and pulmonary suppuration treated with penicillin, *Lancet*, 1945, i, 30-45.
5. DAWSON, M. H., and HOBBY, G. L.: The clinical use of penicillin, observations in one hundred cases, *Jr. Am. Med. Assoc.*, 1941, cxxiv, 10, 611-622.
6. SNOOK, R. R.: Aspiration pneumonia with beginning lung abscess treated with penicillin, *Jr. Kansas Med. Soc.*, 1945, xlv, 40.
7. SMYTH, C. J., and BILLINGSLEA, T. H.: Treatment of lung abscess with penicillin, *Jr. Am. Med. Assoc.*, 1945, cxxix, 15, 1005.

TREATMENT OF VARIOUS INFECTIONS WITH PENICILLIN X, WITH A PRELIMINARY NOTE ON THE VALUE OF PENI- CILLIN X IN SCARLET FEVER *

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PENICILLIN X is a fraction obtained from cultures of the same mold (*Penicillium notatum*) which produces penicillin G (or "regular" penicillin). It differs from penicillin G in the method by which it is extracted, and is usually found more abundantly in flask-grown penicillin. We have tested the relative sensitivity of various bacteria to penicillin X and penicillin G and have found that two to 16 times as much penicillin G is required as penicillin X, unit for unit, to kill many bacteria in vitro. The details of this study will be published elsewhere. Other investigators¹⁻³ have reported similar results. In the present paper we are summarizing the results of the treatment with penicillin X of 104 patients suffering from various diseases.

MATERIAL AND METHODS

The penicillin X † used in this study was the calcium salt. The first batches of penicillin contained about 75 per cent of the X-fraction, and the later batches, 90 per cent. At first we used doses varying from 5,000 to 15,000 units every two or three hours. After studying the serum penicillin concentrations obtained with various doses, we decided upon 50,000 units every six hours as the dose which required a minimum of injections to obtain adequate serum concentrations. Figure 1 compares the mean penicillin concentrations obtained following the intramuscular injection of 50,000 units of penicillin X and crystalline penicillin G. Determinations were made on the sera of at least eight patients receiving each type of penicillin for each time interval. Although the serum concentrations are the same for both types of penicillin one hour after the injections, the serum concentrations are higher for penicillin X than for the penicillin G at similar intervals thereafter. Even more significant is the lack of detectable concentrations of penicillin three hours after an injection of crystalline penicillin G, whereas significant concentrations are obtained with penicillin X for at least six hours, and detectable levels for at least eight hours.

When continuous intramuscular administration was employed, the daily dose was 200,000 to 1,000,000 units, depending upon the severity of the

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† Supplied by Lederle Laboratories, Inc., Pearl River, New York,

disease. The drug was dissolved in 500 to 1,000 c.c. of isotonic sodium chloride solution using the method reported by two of us.⁴ Penicillin X was also administered orally in tablets and capsules containing 25,000 units of the calcium salt and in aluminum hydroxide solution according to the method described by Welch.⁵ The oral dose employed was 100,000 to 200,000 units every two hours.

Comparison of the Mean Penicillin Serum Concentrations Obtained with 50,000 units of Penicillin X and Crystalline Penicillin "G"

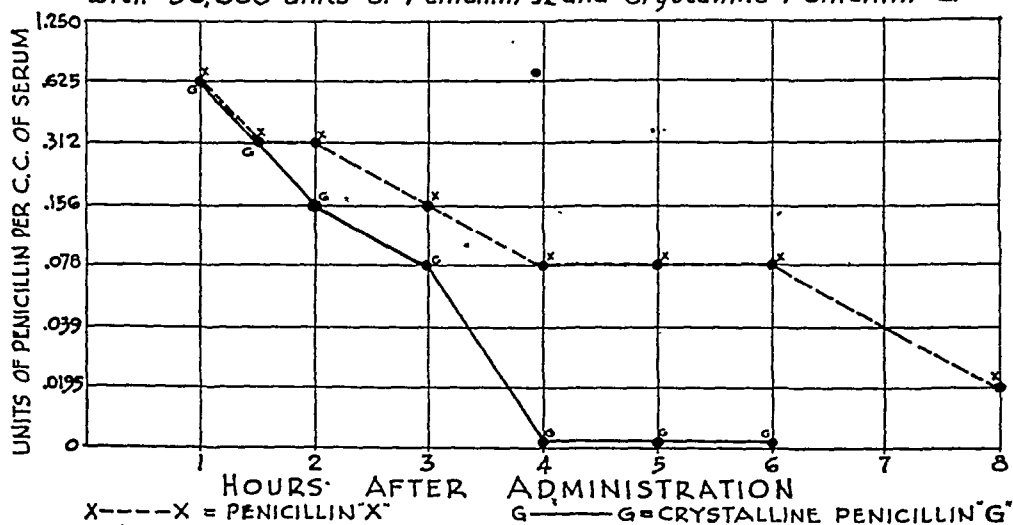


FIG. 1.

RESULTS

The diseases for which penicillin X was used may be divided into two groups (table 1). In Part 1 are tabulated the results observed in a variety of infections in which a specific organism was isolated from the patient. In Part 2 are listed the conditions in which the etiology was unknown.

A group of diseases caused by beta hemolytic streptococci was treated with penicillin X, including 34 patients with scarlet fever, seven with acute pharyngitis, two with suppurative otitis media, three with erysipelas, and two pharyngeal carriers. The use of penicillin in scarlet fever seemed indicated since hemolytic streptococci are highly susceptible to this drug. It was decided to treat with penicillin X all patients with scarlet fever whose temperature was 102° F. or above, who showed evidence of marked toxicity, or who presented complications. Several different dosage-schedules were employed, with 50,000 units every six hours established as the routine dose after trials of 5,000 to 15,000 units every three hours, and single daily injections of 100,000 to 300,000 units. Nearly all patients were treated for five days except a few in whom treatment was continued for several days longer because of persistence of complications present on admission.

The ages of the patients varied from one to 29 years. The number of cases occurring in both sexes and in the white and colored races was essen-

TABLE I
Results of the Treatment of Various Diseases with Penicillin X

	Recovered	Unimproved	Died
<i>Part 1—Infections of Known Etiology</i>			
<i>Beta hemolytic streptococcic Infections</i>			
Scarlet fever.....	33	1	
Streptococcus sore throat.....	7		
Otitis media.....	2		
Erysipelas.....	3		
Streptococcus carriers (pharyngeal).....	2		
<i>Streptococcus viridans Infections</i>			
Bacterial endocarditis.....	1		2
<i>Pneumococcic Infections</i>			
Meningitis.....	2*		2*
Pneumonia.....	4		
<i>Staphylococcic Infections</i>			
Otitis media.....	2		
Otitis externa.....		1	
Abscess.....		1	
<i>Meningococcic Infections</i>			
Meningitis.....	2*	1†	
<i>Gonococcic Infections</i>			
Vaginitis.....	2		
Cervicitis.....	2‡		
Urethritis.....	2‡		
Chronic arthritis.....		1	
<i>H. Influenzae Infections</i>			
Meningitis.....	2§		
<i>Fusospirochetal Infections</i>			
Vincent's angina.....	1	1	
<i>Part 2—Infections of Undetermined Etiology</i>			
<i>Infections of Ear, Nose, and Throat</i>			
Acute pharyngitis.....	5		
Catarrhal otitis media.....	3		
Acute sinusitis.....	1	1	
<i>Infections of the Skin</i>			
Cellulitis.....	6		
Acne vulgaris.....		1	
Abscess.....	1		
<i>Miscellaneous Diseases</i>			
Bronchiectasis.....		1	
Bronchial asthma.....		1	
Infectious mononucleosis.....		1	
Typhoid.....		1	
Inclusion blennorrhea.....		1	
Mikulicz's syndrome.....		1	
Rheumatoid arthritis.....		1	
Epidural abscess and meningitis.....			1
Purulent meningitis.....	1		
Total.....	84	15	5

* Sulfonamides administered concomitantly.

† Sulfonamides administered concomitantly, meningococcic antiserum administered later in the course.

‡ Patients had acute arthritis also, which did not improve under treatment.

§ Sulfonamides and influenzal antiserum administered concomitantly.

tially the same. The admission temperature was 102° F. or over in all patients except five. Three of these five patients had complicating impetigo or abscesses on the hand or foot. The other two patients appeared markedly toxic although their temperatures were slightly below 102° F.

Of the 34 patients so treated, one failed to recover on this therapy alone. Although she received penicillin X for 72 hours, no improvement occurred until 18,000 units of antitoxin were administered. Two patients, who had received single injections of 200,000 and 300,000 units, respectively, improved initially but suffered a recurrence of pharyngitis on the third and eighth hospital days. One made an uneventful recovery after another dose of 200,000 units of penicillin and the other recovered on symptomatic measures. A third patient, who was treated with 50,000 units every six hours, developed a hemolytic streptococcic pharyngitis two weeks after penicillin was discontinued. This disappeared without treatment in two days. No other complications occurred in any of the patients who were given more than one injection. Two of the patients developed sequelae, namely, acute rheumatic fever and acute serous meningitis.⁶ These patients ultimately recovered. In the remaining patients the temperature fell and symptoms disappeared soon after the penicillin X was begun. The time required for the temperature to fall and remain below 99° F. orally or 100° F. rectally, exclusive of fever due to complications, was calculated for each patient. It varied from four to 96 hours, averaging 54 hours. These figures do not include two patients, one of whom was given antitoxin, and the other had a normal temperature on admission and was treated because of the presence of an infected finger.

Nine patients entered with preëxisting complications, consisting in most cases of otitis media and cervical adenitis and infections of the hands or feet. All these complications cleared on penicillin therapy.

The response of patients with other hemolytic streptococcic infections treated with penicillin X was equally as good. The seven patients with acute sore throats exhibited rapid disappearance of fever and local symptoms. Hemolytic streptococci disappeared from their throats within 24 hours after treatment was begun and did not return while the patient was under observation. Similarly, two carriers of beta hemolytic streptococci showed prompt disappearance of the organisms within 24 hours after penicillin X therapy was started. In two patients with purulent otitis media all drainage ceased within 72 hours, and after treatment for seven and nine days, respectively, all evidences of infection had disappeared. There were three patients with erysipelas. They showed a prompt fall in temperature after penicillin was started. The lesions spread slightly during the first 24 hours, but then regressed and healed completely within five to nine days.

Three patients with *Streptococcus viridans* bacterial endocarditis were included in this series. One was treated for 19 days with 200,000 units of penicillin X daily by continuous intramuscular administration. He was admitted with a hemiplegia and known to have neurosyphilis. While under treatment, he developed evidence of a left lower lobe pneumonia and embolization of the right brachial artery. Serum penicillin concentrations were bactericidal for the organism and the blood stream was promptly sterilized, but the patient did not improve and died after 19 days of penicillin treatment.

At autopsy, large friable vegetations were found on a cusp of the aortic valve with perforation of the cusp. The aorta showed syphilitic changes and calcification. There was also evidence of a left lower lobe pneumonia and an embolus in the right brachial artery.

The second patient with endocarditis was a 31 year old colored male who had been ill for five weeks with constitutional symptoms and low grade fever. He had evidence of rheumatic disease with involvement of the mitral and aortic valves. After the organism was isolated, the patient was started on 200,000 units of penicillin X by continuous intramuscular administration. Although the blood stream was apparently sterilized, the patient continued to be febrile and the dose was increased to 500,000 units daily. Fourteen days after treatment was started, the patient had a sudden bout of respiratory distress and died. At autopsy there was evidence of an old active rheumatic myocarditis and endocarditis with rupture of several chordae tendineae of the mitral valve and evidences of congestive heart failure. A healing endocarditis was present on the mitral valve.

The third patient with bacterial endocarditis was treated for eight weeks with 50,000 units of penicillin intramuscularly every six to eight hours. He was admitted with a history of an influenza-like illness of two weeks' duration and a positive blood culture for *Streptococcus viridans* at another hospital. He had findings consistent with rheumatic heart disease with mitral valvulitis. Treatment has now been discontinued for one week and there is no evidence of infection.*

Pneumococci were the etiologic agents in 10 cases. Four patients had meningitis caused by pneumococci of Types 2, 3, 6, and 12 respectively. These patients received 200,000 to 500,000 units daily by continuous intramuscular administration with intrathecal injections of 20,000 units every 12 or 24 hours. In addition, the patients were given sulfonamides in large doses, orally or subcutaneously. In spite of these vigorous measures, two patients died. The spinal fluid was sterilized in both patients before death. Recovery was protracted in a third patient, a 52 year old male admitted in coma. He was found to have bilateral otitis media for which myringotomies were performed. The fourth patient was treated for one day with crystalline penicillin G. Therapy was changed to penicillin X when the infecting pneumococcus was found to be more sensitive to penicillin X than G in vitro. Although clinical improvement and clearing of the spinal fluid were gradual, she apparently recovered completely.

An infant with Type XIV pneumococcic pneumonia recovered coincidentally with penicillin X therapy after she had shown no response to sulfadiazine. Three adult patients with lobar pneumonia were treated with 15,000 units of penicillin X every three hours. Pneumococci, Types 1, 7, and 14, respectively, were isolated from the sputa of the three patients. Treatment was continued for at least 48 hours after the patients were afebrile.

* The follow-up period on this patient is now seven months during which time he has remained well.

The total duration of treatment was seven to 10 days. One patient had involvement of a whole lung plus delirium tremens. All patients made an uneventful recovery.

There were two patients with suppurative staphylococcic otitis media. The response was similar to that reported above in streptococcic otitis media. A patient with chronic bilateral otitis externa of *Staphylococcus albus* origin failed to improve after one week of penicillin X therapy. A hemolytic *Staphylococcus aureus* infection of the scalp with multiple abscesses was treated with penicillin X after sulfonamides and local measures had failed. There was no improvement after one week of treatment with penicillin X or after a longer course of penicillin G which followed.

Three patients with meningococcic meningitis were started on parenteral injections of penicillin X. Sulfadiazine was continued on two patients who had received the drug prior to admission. Both patients made an uneventful recovery, although this outcome might well have been expected from treatment with the sulfonamide alone. The third patient was given sulfonamides and penicillin X on admission because he had been in coma for several days and the prognosis seemed to be extremely grave. Meningococcic antiserum was administered several days later when no improvement was apparent. Death occurred one week after admission.

Gonococci were isolated from seven patients treated with penicillin X. Two children with vaginitis recovered on relatively small doses. Two patients had acute urethritis and complicating arthritis. The urethritis responded to therapy with penicillin X while the arthritis was not affected. On the other hand, in two patients with cervicitis and arthritis, both conditions disappeared after the same treatment. The drug was given to a patient receiving fever therapy for chronic gonococcic arthritis with no apparent effect.

Penicillin X was employed in two cases of *H. influenzae* meningitis in addition to sulfonamides and antiserum. No additional benefit appeared to result from the use of the penicillin X. The bacillus in each case was found to be highly resistant to penicillin in vitro.

Two cases of Vincent's angina were treated with intramuscular penicillin X. One patient showed no improvement with a persistence of the organisms after a single dose of 100,000 units. She recovered later on local measures. The second patient received two 24 hour courses of 300,000 and 100,000 units, respectively, with a one-day interval between courses. Local symptoms improved and the organisms disappeared from the lesions after the first course. However, local therapy was needed to clear the lesions completely.

A group of patients with acute pharyngitis, catarrhal otitis media and acute sinusitis, from whom a definite organism was not isolated, were among the patients treated. All patients recovered promptly except one with acute sinusitis who improved temporarily while on penicillin treatment, but had a return of symptoms the day following discontinuance of the drug.

Six patients with severe cellulitis of the face secondary to trauma, insect bites, infected teeth, impetigo, or infected herpes zoster also recovered.

Penicillin X was used in an attempt to abort an abscess which had developed at the site of an insulin injection. The penicillin X apparently caused an early localization, since on incision only a small amount of sterile seropurulent material drained. The wound healed rapidly after several days more of penicillin X therapy.

A group of patients with a variety of diseases such as acne vulgaris, bronchiectasis, bronchial asthma, infectious mononucleosis, typhoid fever, inclusion blennorrhoea, Mikulicz's syndrome, and rheumatoid arthritis did not improve on doses of penicillin X which were adequate for other infections.

Penicillin X was used in two patients with meningitis secondary to bilateral otitis media from whom no causative organism was isolated from the ears or spinal fluid. One patient recovered on the regime previously described for pneumococcic meningitis plus bilateral myringotomy. In the second patient the otitis media and meningitis cleared after treatment with massive doses of sulfonamides plus parenteral penicillin, but he died following an operation, which included bilateral mastoidectomy and evacuation of an epidural abscess. Autopsy revealed a large cerebellar abscess in addition.

No toxic effects were observed in any patient receiving penicillin X. There were no untoward effects noted after the injection of penicillin X into joint and pleural spaces or the intrathecal space. An occasional patient complained of slight pain at the site of an intramuscular injection.

TABLE II

Comparison of the Course of Scarlet Fever in Patients Receiving Penicillin Compared with Those Treated by Other Measures

Group	Number of patients	Total duration of fever (hours)	Number of patients developing complications after admission
A	34	54	3
B	35	71	11
C	13	74	2
D	34	99	7

Group A—Patients received penicillin X.

Group B—Patients admitted during the same period and treated symptomatically because of the mildness of the disease.

Group C—Patients admitted during the same period and treated symptomatically, or with sulfadiazine for complications, because of delay in diagnosis.

Group D—Patients treated with sulfadiazine and/or antitoxin prior to the period of the use of penicillin.

COMPARISON OF DIFFERENT METHODS OF TREATING SCARLET FEVER

In table 2 we have compared the results of the treatment of our patients with scarlet fever, who received penicillin X (Group A), with the results in three other groups of patients. Included in Group B are all the patients

admitted during the same period as Group A, but who did not receive penicillin X because they did not fulfill the criteria established for penicillin therapy. Group C consists of 13 patients eligible for penicillin, but in whom the diagnosis was not established until the day after admission, and who were, therefore, treated only symptomatically or given sulfonamides if a complication developed. A group of 34 patients with findings similar to those in Group A, who were admitted in the months preceding the use of penicillin, was selected for comparison and is included in Group D. We have compared the total duration of fever in all four groups and found it to be the shortest in the penicillin-treated group, averaging 54 hours. These results compared favorably with 71 hours for the milder untreated patients in Group B and 74 and 99 hours for patients in Groups C and D in whom the illness was as severe as in the patients in Group A. The patients in Group D were admitted during the winter months when the disease is ordinarily more severe, which may account for some of the difference. However, patients in Group C were admitted during the same season as Group D patients and the results are significantly different from the results in Group A, even though the number of patients is admittedly small.

A significant evaluation of the therapy is a comparison of the number of patients developing complications in each group. In the penicillin-treated group only three patients developed complications, two of whom had been inadequately treated. The third patient had a pharyngitis which appeared two weeks after the completion of penicillin therapy and subsided spontaneously in two days. In the 31 remaining patients, who were adequately treated, no complications occurred. In Group B there were 11 patients with complications. Four patients in the group had received antitoxin and one sulfadiazine, and two of the antitoxin-treated patients were among the 11 with complications. Two patients in Group C developed complications and seven in Group D. Among the patients with complications in the last group, four had received either sulfonamides, antitoxin, or both, as did 14 other patients in this group.

Recently Meads and his co-workers⁷ reported their results in a small series of cases of scarlet fever treated with penicillin and other forms of therapy. Their impression was that a more complete and rapid clinical cure occurred in the patients treated with intramuscular penicillin. They noted that although the course of the disease was not significantly altered, no septic complications occurred in this group.

Nine patients in the penicillin-treated group entered the hospital with complications already present. Similarly, five, two, and 12 patients had complications present on admission in Groups B, C, and D. Comparison of the time necessary for these complications to improve showed that the penicillin X-treated patients recovered more rapidly than the others, although the patients in the other groups were treated with sulfadiazine.

There was only one failure in the penicillin-treated group. When the patient showed no improvement after 72 hours of this treatment, she was

given 18,000 units of antitoxin and responded with a prompt drop in temperature and diminution in toxicity. It was later determined that the hemolytic streptococcus isolated from her throat was resistant to the serum penicillin concentrations obtained in the patient.

The ability of penicillin to inactivate the hemolytic streptococcus erythrogenic toxin was studied.⁸ The results showed that the effectiveness of penicillin was not due to neutralization of the toxin.

DISCUSSION

Penicillin X has been used successfully in the treatment of gonococcic¹ and other infections² which are susceptible to penicillin G. We have obtained good results in infections caused by the hemolytic streptococcus, pneumococcus, staphylococcus, and the gonococcus. There was no evidence that it produced any better results than penicillin G in these infections nor that it was effective in other diseases which do not respond to penicillin G. The only clinical evidence of the superiority of penicillin X over penicillin G was that a satisfactory therapeutic response could be obtained when injections of 50,000 units were given as infrequently as every six hours. These results may be explained by the fact that higher and more prolonged serum concentrations of penicillin were usually obtained from the administration of penicillin X than from equivalent doses of penicillin G.

The chief value of penicillin X may be found in infections in which the causative organism is relatively resistant to penicillin G and yet sensitive to penicillin X.

Further clinical observation on a larger number of patients is necessary before the relative value of the two types of penicillin can be completely evaluated.

SUMMARY AND CONCLUSIONS

1. One hundred and four patients with various infections were treated with penicillin X. The results were at least as good as when penicillin G was used.
2. Penicillin apparently decreases the length of the febrile period and reduces the number of complications in patients having scarlet fever.
3. A further trial of penicillin in scarlet fever seems warranted. Further observations are needed to evaluate the relative merits of penicillin X and G in this and in other infections.

We wish to thank the staff of the Georgetown Medical Division for the privilege of reporting several of these cases, and Miss C. Barbara O'Neil and Mrs. Rose Breen for technical assistance.

BIBLIOGRAPHY

1. WELCH, HENRY, PUTNAM, L. E., RANDALL, W. A., and HERWICK, R. P.: Penicillin X: Successful treatment of gonorrhea with a single intramuscular injection, Jr. Am. Med. Assoc., 1944, cxxvi, 1024.

2. ORY, E. M., MEADS, M., and FINLAND, M.: Penicillin X: Comparison with penicillin G with respect to sensitivity of pathogenic organisms and serum levels, Jr. Am. Med. Assoc., 1945, cxxix, 257.
3. LIBBY, R. L., and HOLMBERG, N. L.: The activity of penicillin G and X in vitro, Science, 1945, cii, 303.
4. HIRSH, H. L., and DOWLING, H. F.: Observations on the continuous intramuscular method of administering penicillin, Am. Jr. Med. Sci., 1945, ccx, 435.
5. WELCH, HENRY, PRICE, C. W., and CHANDLER, V. L.: Prolonged blood concentrations after oral administration of modified penicillin, Jr. Am. Med. Assoc., 1945, cxxviii, 845.
6. SWEET, L. K., and LEPPER, M. H.: Acute serous meningitis in scarlet fever, Jr. Pediat., 1944, xxiv, 295.
7. MEADS, M., FLIPSE, M. E., JR., BARNES, M. W., and FINLAND, M.: Penicillin treatment of scarlet fever, Jr. Am. Med. Assoc., 1945, ccxxiv, 785.
8. DOWLING, H. F., and HIRSH, H. L.: The inability of penicillin to inactivate streptococcus erythrogenic toxin. To be published.

SERUM AMYLASE AND SERUM LIPASE IN MUMPS *

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THE recent valuable reports of Zelman ¹ and Applebaum ² on serum amylase in mumps appeared while we were engaged in carrying on studies of mumps and its complications. We became particularly interested in testing whether or not elevated serum amylase values could be of assistance in aiding in the diagnosis of orchitis and epididymitis due to mumps when there was no history or evidence of parotitis.³ The additional problem of attempting to determine the effect of mumps on serum lipase presented itself, for if, as some investigators ^{4, 5} believe, the serum amylase elevation noted in mumps is due to a silent pancreatitis, it would be reasonable to expect concomitant elevation in serum lipase. Zelman considered this last problem but abandoned it because of objections to the method ordinarily used to determine serum lipase.

The origin and function of serum amylase is not known.^{6, 7} Ligation of the parotid duct results in an increase of serum amylase.⁷ Pancreatic duct ligation is likewise followed by an elevation of serum amylase in the blood, but it returns to normal in 8 to 15 days.⁹ The following conditions have also been found to cause elevated values of serum amylase: acute pancreatitis ^{2, 6, 7, 8, 9, 10}; perforation of peptic ulcer into or near the pancreas ^{6, 10}; trauma to pancreas (experimental) ⁷; parotitis ^{1, 2, 10}; increased thyroid activity.¹¹ Age, sex, diet, vitamin deficiency and starvation do not affect serum amylase.^{7, 10} Patients with liver disease have amylase values which tend to be low.^{9, 10} Nevertheless, the liver contains no amylase.⁷ Diseases of carbohydrate metabolism have normal values.⁸ However, Heifetz et al. have reported that the diastatic activity of the blood is lower in the more severe diabetics.¹⁰ Amylase (diastase) is excreted by the kidneys.¹² Thus impaired amylase excretion has been noted in renal insufficiency.^{10, 13}

The method of Somogyi ¹⁴ was employed since it is the one standard at the Naval Medical School.¹⁵ The principle involved is the hydrolysis of a starch solution by amylase in the serum. After incubation of the starch mixture for a definite period, it is added to an iodine solution to determine the end point for complete hydrolysis. The end point is an absence of blue. The results are reported in terms of units. The normal range is up to 320 units.

Fifty-four normal adults were used to determine the normal range. Table 1 shows the results obtained.

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From the U. S. Naval Training Center, Gulfport, Mississippi.

The views expressed herein are the opinions of the writers and not necessarily the views of the Bureau of Medicine and Surgery or the Navy at large.

TABLE I

Units	Frequency
228	24
266	10
320	18
400	2

Our results corresponded well with the usual values found.

The experimental group consisted of 224 mumps patients of whom 68 developed orchitis and epididymitis. Six hundred eighty-four serum amylase determinations were done. An initial determination was done usually on the day of, or on the day after admission. Each patient had a serum amylase test repeated approximately one week after admission and often an additional one on the day of discharge. The average period of hospitalization was terminated on the fourteenth day of disease. Some patients were carried over to the fifteenth to seventeenth day of disease owing to local regulations for days of discharge. Table 2, which follows, contains in the

TABLE II

Serum Amylase Determinations in Mumps

Serum Amylase in Units	Day of Disease*				
	1-7	8-14	15-21	22-32	Total
228	11	21	25	11	68
266	5	7	14	3	29
320	27	44	35	15	121
400	35	46	16	4	101
533	47	60	9	6	122
800	61	39	7	1	108
1600	79	51	5	0	135
Total	265	268	111	40	684
% Serum Amylase values above-normal, i.e. 400 and over	83.77%	73.13%	33.33%	27.50%	

* Calculated from day of onset of symptoms, not necessarily from day of admission to the sick list.

column headed 15 to 21 day determinations obtained from some of these carry-overs, but the greater number is made up of determinations done on patients who had developed orchitis as a complication. In the fourth week and over group (22 to 32 day) appear values obtained almost entirely from patients who had orchitis as a complication. Of the 224 patients, 86½ per cent were 17 through 23 years of age; 13½ per cent were 24 through 39 years of age.

It may be seen from table 2 that during the first week of the disease, 83.77 per cent of all determinations show an elevated serum amylase. There were 43 patients who had normal serum amylase values in the first week of

the disease. Thirty-three of these 43 showed elevated values in the second week of the disease. Thus 96.22 per cent of all mumps patients had elevations of serum amylase some time during the first two weeks of the disease. This confirms the observations of Applebaum.² It may be that if more observations on serum amylase had been done on the 10 patients whose amylase values remained normal, elevations would have been recorded. Further study of table 2 shows that there is a progressive decrease in the levels of serum amylase from week to week.

Lewison⁹ observed 13 cases of mumps. No effect was noted on the serum amylase of the patients who developed orchitis. Murphy et al.¹⁶ reported a similar experience in their observations on seven cases of orchitis complicating 35 cases of mumps.

Table 3 analyzes the values of serum amylase in 68 cases of orchitis and epididymitis which complicated the 224 patients with mumps, under study. All the values noted are determinations made after the appearance of orchitis and epididymitis. The 68 cases are arranged in groups according to the day of onset of the complication, i.e. 1-7 day; 8-14 day; 15-17 day. No case of orchitis occurred later than 17 days after the onset of mumps. The serum amylase determinations are arranged in groups of weeks (1-7 day; etc.) according to the time the determinations were done in relation to the day of disease. These values are compared with determinations done on the cases of uncomplicated mumps plus the cases of mumps before the appearance of the complication.

It may be seen from table 3 that serum amylase values in mumps orchitis parallel the values in uncomplicated mumps. It is evident that the elevations of serum amylase are a function of the disease associated with the parotitis alone. Hence, as a clinical aid in establishing the etiology of an orchitis and epididymitis, the serum amylase would be of limited value. There are two types of orchitis and epididymitis due to mumps which may present themselves for diagnosis. The first type follows a parotitis which goes unnoticed by the patient and perhaps not observed by the examiner. Here, the value of serum amylase would depend upon how soon the orchitis developed after the onset of the missed parotitis. The later the orchitis developed, the less the chance that the serum amylase would be elevated. The second type is the true primary orchitis which occurs without the appearance of parotitis. In this second type serum amylase determination would probably be entirely normal. This will be discussed later after consideration of serum lipase in mumps. The finding of an increased serum amylase in a case of orchitis would point towards mumps as the etiologic factor. A normal serum amylase would not necessarily rule out mumps. One would then have recourse to other aids such as (a) careful history of contact, (b) lumbar puncture and cell count on spinal fluid.^{3, 17}

A number of patients were encountered with conditions other than mumps in which there was swelling of the face or neck, often in the parotid region. Serum amylase determinations were made on them to determine

TABLE III

Analysis of Serum Amylase after the Appearance of Orchitis and Epididymitis

Day of Occurrence of Orchitis and Epididymitis	Number of Cases		Day of Disease			
			1-7	8-14	15-21	22-32
1-7	43	No. Amylase Determinations	38	50	38	22
		% of Values 400 Units or More	81.57%	58.0%	34.42%	28.51%
8-14	19	No. Amylase Determinations		16	16	(b) 8
		% of Values 400 Units or More		62.5%	31.25%	(50%)
15-17	6	No. Amylase Determinations			6	(b) 7
		% of Values 400 Units or More			0.0%	0.0%
Uncomplicated Mumps Including Mumps Cases before Development of Orchitis and Epididymitis	(a) 211	No. Amylase Determinations	227	202	51	(b) (c) 3
		% of Values 400 Units or More	84.14%	77.22%	37.05%	33.33%

(a) 13 cases were admitted with orchitis and parotitis.

(b) % calculated from these small groups are of very limited value.

(c) 3 patients with uncomplicated mumps, who developed mumps while convalescing from another condition.

the specificity of the elevations noted in mumps. Table 4 lists the conditions and the amylase findings.

TABLE IV

Other Conditions with Swelling of Face or Neck

Diagnosis	Number of Cases	Units Serum Amylase
1. Lymphadenitis secondary to scarlet fever	12	320 or less
2. Lymphadenitis secondary to tonsillitis	3	320 or less
3. Cellulitis of face following antrum perforation during treatment for sinusitis	1	266
4. Impacted molar tooth with swelling over mandible	1	200
5. Fracture of mandible with swelling in parotid region	1	320
6. Recurrent submaxillary gland swelling secondary to duct stenosis	1	320
7. Lymphadenitis secondary to scarlet fever	1	400
8. Lymphadenitis secondary to peritonsillar abscess	1	533
9. Facial diphtheria with "bull neck"	1	400
10. Diphtheria with cervical lymphadenitis and slight soft tissue edema	1	533

Of 17 cases of lymphadenitis listed in table 4 only two cases showed elevated values. These determinations were not repeated, hence the two

elevations are open to some question. Of interest is the case of recurrent submaxillary gland swelling with normal serum amylase. The findings in our two cases of diphtheria were striking. More determinations are required of the conditions listed above to determine the specificity of serum amylase determinations in swelling of the face and neck. This is particularly true of diphtheria with edema of the face and neck ("bull neck"). Applebaum² noted three cases of extra-parotid mumps with normal amylase values. Two involved the submaxillary glands and one involved the sublingual glands. He explained these findings by pointing out that parotid saliva is particularly rich in salivary amylase as compared to the other salivary glands. Since the damming-back of amylase into the blood stream in cases of parotid inflammation is thought to be a mechanism by which the blood serum amylase is raised, high values would be expected in parotid mumps and low ones in submaxillary or sublingual mumps. Lewison⁹ found normal serum amylase values in 94 per cent of 720 patients having clinical conditions other than mumps and diseases of the biliary system.

Serum lipase is not affected by food or starvation.⁶ It is increased in pancreatitis,⁶ duodenal ulcer perforating into the pancreas,⁶ pressure of tumor arising in or near the pancreas such as enlargement of lymph nodes near the head of the pancreas,¹⁸ pancreatic lithiasis in which a stone blocks one of the pancreatic ducts.¹⁸ Lewison states that in his limited experience with the serum lipase test, its activity parallels that of serum amylase in pancreatic disease. But he states it takes 24 hours for the elevated lipase to appear in acute pancreatitis. This fact diminishes its usefulness in clinical emergencies.⁹ Johnson and Bockus¹⁸ emphasize the specificity of hyperlipasemia in pancreatic disease.

The serum lipase method employed in this study, recommended by the Naval Medical School,¹⁹ is a modification of the method of Lovenhart by Cherry and Crandall as used by Comfort and Osterberg.²⁰ It depends on the estimation of fatty acid which results from the hydrolysis of an olive oil emulsion by the blood serum lipase which acts on the oil over a 24 hour period under fixed conditions of hydrogen-ion concentration and temperature. The fatty acid is titrated against N/20 sodium hydroxide. The normal range is given as 0.0 c.c. to 1.5 c.c. of N/20 NaOH.^{6, 19} However, Johnson and Bockus using this method have found that the normal values are less than 1.00 c.c. N/20 NaOH.²¹ In our study, normal men showed serum lipase values less than 1.00 c.c. of N/20 NaOH.

Serum lipase determinations were done on 54 normal men in the same age group as those patients who were treated for mumps. Table 5 records our findings.

The normal mean was found to be 0.309 ± 0.016 c.c. of N/20 NaOH with a standard deviation 0.184 ± 0.012 c.c. N/20 NaOH. The range is calculated to be 0.00 to 0.86 c.c. This upper limit of normal is closer to the value noted by Johnson and Bockus (i.e. value less than 1.00 c.c. for upper normal).^{18, 21}

TABLE V
Serum Lipase in Normal Men

Serum Lipase in c.c. N/20 NaOH	Frequency
0.00	0
0.05	4
0.10	5
0.15	8
0.20	10
0.25	0
0.30	3
0.35	2
0.40	6
0.45	2
0.50	2
0.55	2
0.60	4
0.65	1
0.70	1

Table 6 was compiled from 671 determinations of serum lipase done on 224 cases of mumps.

TABLE VI
Serum Lipase in 224 Cases Mumps

Serum Lipase in c.c. N/20 NaOH	Frequency				Total
	Day of Disease				
	1-7	8-14	15-21	22-32	
0.00	3	12	2	2	19
0.05	6	3	2	0	11
0.10	46	24	26	7	103
0.15	23	16	6	3	48
0.20	45	42	13	6	106
0.25	14	24	4	1	43
0.30	27	30	12	3	72
0.35	7	9	5	5	26
0.40	21	25	6	3	55
0.45	10	7	3	3	23
0.50	14	12	6	3	35
0.55	7	9	4	2	22
0.60	18	12	6	0	36
0.65	2	5	6	0	13
0.70	3	7	5	1	16
0.75	0	1	1	0	2
0.80	2	6	0	0	8
0.85	0	1	0	0	1
0.90	4	1	2	0	7
0.95	0	1	0	0	1
1.00	5	2	2	1	10
1.05	0	0	0	0	0
1.10	5	4	0	0	9
1.15	0	0	0	1	1
1.20	1	2	0	0	3
1.25	1	0	0	0	1
Total	264	255	111	41	671

The average serum lipase with its standard deviation was calculated for each time unit noted in table 6. Table 7 contains a summary of these calculations as well as the average calculated from serum lipase determinations done on 54 normal men.

TABLE VII

Summary of Serum Lipase Determinations in Terms of c.c. N/20 NaOH Done on 54 Normal Men and 224 Patients with Mumps

		Number of Determinations	Mean	Standard Deviation
	Normal Group	54	0.309 \pm 0.016 c.c.	0.184 \pm 0.012 c.c.
Mumps (224 patients)	1-7 day	264	0.334 \pm 0.010 c.c.	0.2439* \pm .0068 c.c.*
	8-14 day	255	0.349 \pm 0.010 c.c.	0.2438 \pm .0072 c.c.
	15-21 day	111	0.333 \pm 0.015 c.c.	0.234 \pm 0.010 c.c.
	22-32 day	41	0.323 \pm 0.024 c.c.	0.236 \pm 0.017 c.c.
	Total Mumps	671	0.3365 \pm 0.0062 c.c.	0.2412 \pm 0.0044 c.c.

* Reasons for retention of decimals in published biometric-constants are set down by Raymond Pearl.²²

The means noted in table 7 show relatively slight differences. The greatest difference lies between the normal mean 0.309 ± 0.016 c.c. and that noted in the group 8-14 day, 0.349 ± 0.010 c.c. x/d calculated for the difference between these two means was approximately 0.66. This denotes that there is no significant difference between them. The means of the remainder of the groups likewise showed no significant difference from the mean of the normal group.

The upper limit of serum lipase in our control normal group was 0.86 c.c. of N/20 NaOH. In the 671 determinations done on our mumps patients, there were 27 patients who showed serum lipase values of 0.90 to 1.25 c.c. of N/20 NaOH somewhere in the course of their illness. A careful review of the charts of these patients showed that not a single one had any evidence of acute pancreatitis. One patient had an episode of vomiting associated with fever at the onset of orchitis. The nurses' notes on another patient showed that he had an "upset stomach" on admission. Both of these patients were seen at least twice daily from the day of admission to the day of discharge and in neither was there any complaint of abdominal pain or evidence clinically of pancreatitis. Thus in the 27 patients (32 lipase determinations above 0.85 c.c.) with slightly elevated serum lipase values, there was no clinical pancreatitis present. In the remainder of the mumps patients with normal serum lipase there was likewise no case of clinical pancreatitis.

Hyperlipasemia is said to be specific for acute pancreatitis.¹⁸ Values as high as 12.0 c.c. of N/20 NaOH have been reported in acute pancreatitis.⁹

Johnson and Bockus have found abnormal values ranging from 1.0 to 10.0 c.c.¹⁸ Hence, since our upper normal was 0.86 c.c. of N/20 NaOH, the maximum number of patients who could have had a silent pancreatitis was 27. We must conclude, therefore, that "silent pancreatitis" if it exists at all, is the exception and not the rule.

The great majority of the 224 patients under study showed an elevation of serum amylase with normal serum lipase. It must hold then that these elevations of serum amylase are extra-pancreatic in origin. This is likewise borne out by other facts such as (a) the finding of an elevated serum amylase in

- (1) Ligation of the parotid duct.⁷
- (2) Calculous obstruction of the salivary duct.¹⁰
- (3) Suppuration of the salivary gland.¹⁰

(b) The finding of normal amylase values in extra-parotid mumps involving the submaxillary or submental glands.²

To return to a problem mentioned above, it is evident that, in primary orchitis and epididymitis unassociated with involvement of the parotid gland but secondary to systemic mumps, the serum amylase determination would be expected to fall in the normal range. An elevated serum amylase would point to a missed parotitis with systemic mumps.

CONCLUSIONS

1. Serum amylase determinations are of value in the differential diagnosis of parotitis.

2. 96.22 per cent of 224 patients with mumps showed elevations of serum amylase in the course of the disease.

3. In the first week of disease 83.77 per cent of the mumps patients showed elevations of serum amylase. This percentage fell progressively week by week so that in the fourth week (actually 22-32 day) 27.5 per cent of patients still showed elevated values of serum amylase.

4. Elevations of serum amylase apparently follow the evolution of the parotitis.

5. The appearance of orchitis and epididymitis as complications of mumps does not affect the amylase of the serum. Hence in apparently primary acute orchitis or epididymitis of mumps origin, the elevation of serum amylase will depend upon how soon the orchitis and epididymitis follow the original parotitis (which may have been overlooked by the patient or missed by the examiner). In true primary orchitis and epididymitis of systemic mumps origin unassociated with parotitis, normal values of serum amylase may be anticipated.

6. Elevated serum amylase found in uncomplicated mumps is extra-pancreatic in origin.

7. 89.5 per cent of 224 mumps patients had normal serum lipase values. 11.5 per cent of patients had slightly elevated values. None was greater

than 1.25 c.c. of N/20 NaOH and none showed any clinical evidence of pancreatitis.

BIBLIOGRAPHY

1. ZELMAN, SAMUEL: Blood diastase values in mumps and mumps pancreatitis, *Am. Jr. Med. Sci.*, 1944, ccvii, 461-464.
2. APPLEBAUM, I. L.: Serum amylase in mumps, *Ann. Int. Med.*, 1944, xxi, 35-43.
3. CANDEL, SAMUEL, WHEELOCK, MARK C., and GRIMALDI, GREGORY J.: Mumps orchitis with a discussion of plasma prophylaxis, *U. S. Naval Med. Bull.*, 1945, xlv, 97-107.
4. FENNEL, ERIC: Amylase determinations, *Am. Jr. Clin. Path.*, 1944, xiv, 89-102.
5. BODANSKY and BODANSKY: *Biochemistry of disease*, 1940, The Macmillan Company, N. Y., p. 277.
6. COMFORT, M. W., and OSTERBERG, A. E.: Serum amylase and serum lipase in the diagnosis of disease of the pancreas, *Med. Clin. North Am.*, 1940, xxiv, 1137-1149.
7. SOMOGYI, MICHAEL: Diastatic activity of human blood, *Arch. Int. Med.*, 1941, lxvii, 665-679.
8. SORKIN, S. Z.: Blood amylase activity in disease of carbohydrate metabolism and in non-diabetic pancreatic disease, *Jr. Clin. Invest.*, 1943, xxii, 329-333.
9. LEWISON, EDWARD F.: Clinical value of the serum amylase test, *Surg., Gynec. and Obst.*, 1941, lxxii, 202-212.
10. HEIFETZ, C. J., DROBSTEIN, J. G., and GRAY, S. H.: Clinical studies on blood diastase, *Arch. Int. Med.*, 1941, lxvii, 819-827.
11. BARTLETT, WILLARD, JR.: Effects upon blood amylase in thyroid activity, *Proc. Soc. Exper. Biol. and Med.*, 1937, xxxvi, 843-848.
12. DUNLOP, G. A.: The diastatic index in acute parotitis, *Lancet*, 1933, ii, 183-184.
13. POLOWE, DAVID: Blood amylase, *Am. Jr. Clin. Path.*, 1943, xiii, 288-301.
14. SOMOGYI, MICHAEL: Micromethods for the estimation of diastase, *Jr. Biol. Chem.*, 1938, cxxv, 399-414.
15. Naval Medical School: Blood chemistry (clinical chemistry). Part I, *Nat. Naval Med. Center, Bethesda, Md.*, p. 80-82.
16. MURPHY, J. P., BOZALIS, G. S., and BIERI, E. J.: Blood diastase in mumps, *Am. Jr. Dis. Child.*, 1943, lxvi, 264-266.
17. CANDEL, SAMUEL, WHEELOCK, MARK C., TURK, JOHN P., and SMOOT, JOHN L.: Mumps meningitis, *U. S. Nav. Med. Bull.*, 1944, xlii, 861-870.
18. JOHNSON, T. A., and BOCKUS, H. L.: Present status of serum lipase test, *Am. Jr. Digest. Dis.*, 1943, x, 1-7.
19. Naval Medical School: Blood chemistry (clinical chemistry). Part I, *Nat. Naval Med. Center, Bethesda, Md.*, p. 83-86.
20. COMFORT, M. W., and OSTERBERG, A. E.: Lipase and esterase in blood serum: their diagnostic value in pancreatic disease, *Jr. Lab. and Clin. Med.*, 1934, xx, 271-278.
21. JOHNSON, T. H., and BOCKUS, H. L.: Diagnostic significance of determinations of serum lipase, *Arch. Int. Med.*, 1940, lxvi, 62-78.
22. PEARL, RAYMOND: *Introduction to medical biometry and statistics*, 1940, W. B. Saunders Co., Philadelphia.

THE PROTHROMBINOPENIC EFFECT OF MASSIVE SALICYLATE THERAPY IN ACUTE RHEUMATIC FEVER *

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FOLLOWING the appearance of Coburn's report ¹ advocating large doses of salicylates in rheumatic fever, interest in the problem of salicylate intoxication has increased and warnings have been sounded regarding the dangers of salicylate therapy.^{2, 3} Stress has been laid upon hemorrhage as one of the most striking of these complications, and case reports are cited of deaths from hemorrhage, but prothrombin levels were not determined in any of the fatal cases reported.^{4, 5}

Quick questioned the rôle of salicylate hypoprothrombinemia in the production of fatal hemorrhage, on the grounds that no evidence had been offered that prothrombin levels could be sufficiently reduced by salicylates to cause hemorrhage.⁶ Recently, Fashena and Walker ⁷ reported prothrombin times of 60 to 90 seconds in six children treated with large doses of salicylates, but made no mention of hemorrhage occurring in these patients.

It is considered of interest, therefore, to report the following study, which was undertaken to determine the behavior of prothrombin in adults treated with large doses of salicylates.

The subjects were 25 cases of acute rheumatic fever, treated by Coburn's method. Their ages ranged from 18 to 40. All had been hospitalized for rheumatic fever in an acute phase.

METHODS

The patients were given 10 grams of sodium salicylate in 1,000 c.c. of normal saline intravenously over a four hour period daily for six days or longer, depending on the patient's clinical course. Those patients who failed to show a prompt response in symptoms, fever, and sedimentation rate were given an additional 10 grams of sodium salicylate daily. Thereafter, 10 grams of the drug were given orally each day in divided doses at four hour intervals. Duration of treatment varied from 21 to 60 days depending on the patient's response to therapy.¹ Daily physical examinations were made, a four hour temperature chart was kept, erythrocyte sedimentation rate (Cutler), complete blood count and urinalyses were determined at least every third day.

The Magath modification of the Quick method of determining the prothrombin time was used.⁸ Thromboplastin was obtained from fresh rabbit brain; each prothrombin time determination was checked by a normal con-

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trol. By this technic, normal plasma clots in 18 to 22 seconds. In each instance, the prothrombin time was obtained before salicylates were administered, and was repeated at least every third day while the patient was undergoing treatment.

Quantitative blood salicylate analyses were made at three day intervals throughout the period of therapy.¹ Determinations were made in the mornings prior to any intravenous salicylate administration and so during the period of intravenous therapy represented the drug concentration residual after the previous day's administration. The levels obtained during oral therapy were uniformly higher than the residual levels during parenteral administration. Concentrations of drug were maintained at about 35 mg. in almost all cases. In only three cases was the maximum salicylate concentration under 40 mg. per cent; in 18 the levels ranged from 40 to 49, and in six the levels exceeded 50.

Because of the known effect of liver disease on the prothrombin level of the blood,⁹ efforts were made to eliminate this factor. No history suggestive of hepatic disease was obtained from any of the patients studied. Cephalin cholesterol and intravenous hippuric acid tests were performed on each patient before and after salicylic acid therapy with entirely normal results.

RESULTS

Two effects of massive salicylate dosage on the blood prothrombin were noted. A moderate reduction of prothrombin to 55 to 75 per cent of normal occurred in all cases after the third or fourth day of treatment. In addition, a maximum effect, of short duration, was observed to occur in a number of cases. The range of this peak effect is indicated in table 1.

TABLE I
Maximum Prothrombin Depression (Percentage of Normal)

Prothrombin	10-19%	20-29%	30-39%	40-49%	50-59%	60-100%
No. of Cases	2	10	4	5	6	0

It will be noted that two cases fell below the critical level of 20 per cent prothrombin, and 12 cases, or almost half the total, reached levels below 30 per cent of normal.

In two cases a second course of treatment was required. In both instances the hypoprothrombinemia was less than that observed during the original course of massive therapy.

Of interest was the variation in the time of appearance of the maximum hypoprothrombinemic effect in the series (table 2).

TABLE II
Time at Which Maximum Reduction of Prothrombin Occurred

Max. Hypoprothrombinemia	1st Wk.	2nd	3d	4th	5th	6th Wk.
No. of Cases	1	9	9	1	3	4

The duration of pronounced prothrombin depression was observed to be from one to three days in all cases except two in which the effect was greatest. In these two cases, the marked prothrombin depression lasted from three to six days. Despite continuation of salicylates, there was a spontaneous and rather rapid return of the prothrombin time toward normal levels. This tendency, so marked following the maximum depression of prothrombin, was noted as a general trend following the third week of therapy, when the prothrombin time approached normal values despite the maintenance of high levels of salicylate concentration in the blood (chart 1).

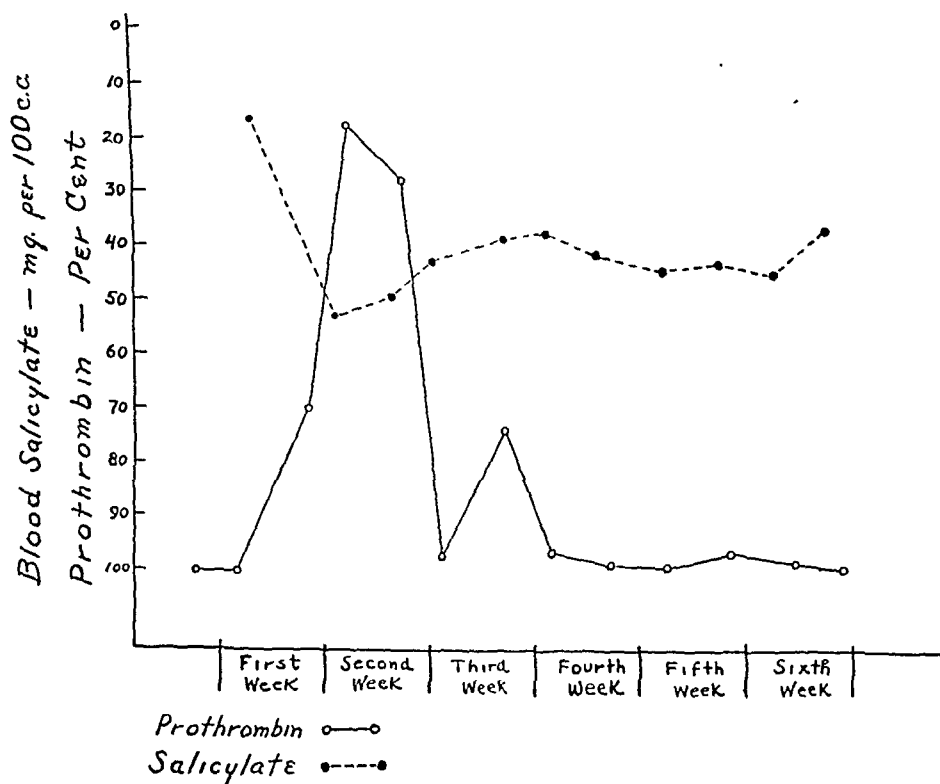


CHART 1. Relation of blood salicylate level to the degree of prothrombin deficiency.
(Illustrative case)

The exception to this trend was in those cases in which the maximum hypoprothrombinemia was late in appearing (seven cases). These, however, showed the same trend toward normal levels of prothrombin concentration at a similar interval following the peak effect.

Evidence of bleeding was sought carefully in each case. Five patients developed epistaxis, which was severe in only one case. Two of the five also showed small splinter hemorrhages under the finger nails. These hemorrhages have been observed by us and others in patients undergoing dicoumarol therapy. The patient with severe epistaxis had a prothrombin percentage of 24 per cent of normal. Those with both epistaxis and splinter hemorrhages had prothrombin percentages of 16 and 22 per cent at the time

the bleeding occurred. In the remaining cases of epistaxis, prothrombin percentages ranged from 21 to 28 per cent of normal. In all instances, salicylate therapy was continued, and the bleeding was controlled by ordinary measures. Spontaneous return of prothrombin time to normal was observed in these patients as well as in all others in the group. No instance of bleeding was observed after the third week of treatment.

In a series of rheumatic fever patients treated by penicillin, without salicylates, and under rigid controls, no hypoprothrombinemia nor bleeding was observed.

In brief, hypoprothrombinemia of some degree occurred early in all cases treated with massive doses of salicylate. A more marked depression was noted in some cases. This effect occurred abruptly, was of short duration, returning spontaneously toward normal levels usually within three days. The marked prothrombin depression occurred any time during treatment from the first through the sixth week. However, in the majority of cases, it occurred during the first three weeks of treatment.

In 12 cases the prothrombin level dropped below 30 per cent of normal. In five cases bleeding, consisting of epistaxis or small nail bed hemorrhage, occurred at the time of maximum prothrombin depression.

DISCUSSION

The prothrombinopenic effect of salicylic acid was first demonstrated by Link and his associates¹⁰ in the rat, after their chemical studies had shown that salicylic acid was an important degradation product of the hemorrhagic agent 3, 3' methene bis(4 hydroxycoumarin).^{11, 12}

Meyer¹³ and Shapiro⁹ independently reported hypoprothrombinemia following administration of salicylates in man. Both found that synthetic vitamin K counteracted this effect. Rapoport et al. reported prothrombin depression in rheumatic children treated with salicylates.¹⁴ In their series the greatest prolongation of prothrombin time was 35 seconds. However, Coburn in his original series, reported no change in the prothrombin time.¹ More recently others have reported complete absence of prothrombin effect in salicylate treated patients.¹⁵ Possible explanation for these divergent results is offered by the present series of cases in which the marked hypoprothrombinemia was found to be of short duration, and occurred at almost any time during the course of treatment.

Butt's study¹⁶ in which he reported uniform but only moderate prothrombin depression by salicylates is difficult to compare with the present study. His patients were given gradually increasing doses of salicylates, rather than massive doses at the outset, as in the present series. Moreover, the majority of Butt's patients were convalescent, whereas all our patients were in an acute phase of rheumatic fever with possible depletion of their vitamin K stores as a consequence.

This latter factor may account for the more profound prothrombin depression noted in some of our patients, as well as for the individual variation

in time of occurrence and degree of severity of the marked prothrombin depression.¹⁷

The five cases reported here of bleeding occurring at the time of maximum hypoprothrombinemia induced by salicylates, are the only ones thus far reported to our knowledge. Moreover, it must be stressed that in these cases the prothrombin returned spontaneously to normal levels during continued administration of salicylates, and with its return, the bleeding tendency stopped. The uniformity with which this occurred, together with the general tendency, noted above, for prothrombin levels to return to normal during the course of therapy in all the cases studied, suggests that hypoprothrombinemia as a cause of serious hemorrhage in salicylate treated patients is an unlikely occurrence. However, should operation be contemplated in such patients the added risk of hemorrhage warrants the use of vitamin K.

The mechanism by which salicylates reduce the prothrombin content of the blood is not clear. Link suggested that a parallelism exists between the effect of dicoumarol and that of salicylates.¹⁰ Doubt is cast upon this relationship by the transient character of the prothrombinopenia in our cases during the continued administration of salicylates, as well as by the suggestion of development of tolerance to the drug indicated by the general trend toward normal prothrombin levels after the third week of treatment. These observations, together with our failure to demonstrate evidence of liver damage, argue against toxic action of salicylates on the liver with resultant prothrombin depression.¹⁸ Further studies of the metabolism of salicylic acid will be required before the precise mechanism of its effect on prothrombin can be determined.

SUMMARY

1. Hypoprothrombinemia of varying degree occurred in 25 cases of acute rheumatic fever treated with massive doses of sodium salicylate.
2. In five cases, bleeding, consisting of epistaxis or small nail bed hemorrhage, occurred at the time of maximum prothrombin depression.

ADDENDUM

Since this paper was submitted, Clausen and Jager¹⁹ have reported a case in which bleeding from the nose and gums occurred in the presence of hypoprothrombinemia induced by salicylates.

Their observation that spontaneous hemorrhage due to the prothrombinopenic effect of salicylates is rare and, when present, is apparently not a factor in causing death from salicylate intoxication, bears out our opinion.

BIBLIOGRAPHY

1. COBURN, A. F.: Salicylate therapy in rheumatic fever, *Bull. Johns Hopkins Hosp.*, 1943, lxxiii, 435.
2. Editorial: Is aspirin a dangerous drug? *Jr. Am. Med. Assoc.*, 1944, cxxiv, 777.
3. Editorial: Hazards in the salicylate treatment of rheumatic fever, *Jr. Am. Med. Assoc.*, 1945, cxxvii, 460.
4. ASHWORTH, C. T., and MCKEMIE, J. F.: Hemorrhagic complications with death probably from salicylate therapy, *Jr. Am. Med. Assoc.*, 1944, cxxvi, 806.

5. TROLL, MARY M., and MENTLN, MAUD L.: Salicylate poisoning, *Am. Jr. Dis. Child.*, 1945, lxi, 37.
6. QUICK, A. J.: Correspondence, *Jr. Am. Med. Assoc.*, 1944, cxxvi, 1167.
7. FASHENA, G. J., and WALKER, J. N.: Salicylate intoxication: studies on the effects of sodium salicylate on prothrombin time and alkali reserve, *Am. Jr. Dis. Child.*, 1944, lxxviii, 369.
8. MAGATH, T. B.: Technic of the prothrombin time, *Am. Jr. Clin. Path.*, 1939, ix (Tech. suppl.) 187.
9. SHAPIRO, S., REDISH, M. H., and CAMPBELL, H. A.: Studies on prothrombin. IV. The prothrombinopenic effect of salicylates in man, *Proc. Soc. Exper. Biol. and Med.*, 1943, liii, 251.
10. LINK, K. P., OVERMAN, R. S., SULLIVAN, W. R., HUEBNER, C. F., and SCHEEL, L. D.: Studies on the hemorrhagic sweet clover disease. XI. Hypoprothrombinemia in the rat induced by salicylic acid, *Jr. Biol. Chem.*, 1943, cxlvi, 463.
11. STAHMANN, M. A., HUEBNER, C. F., and LINK, K. P.: Studies on the hemorrhagic sweet clover disease. V. Identification and synthesis of the hemorrhagic agent, *Jr. Biol. Chem.*, 1941, cxxxviii, 513.
12. HUEBNER, C. F., and LINK, K. P.: *Ibid.*, 1941, cxxxviii, 529.
13. MEYER, O. O. and HOWARD, B.: Production of hypoprothrombinemia and hypocoagulability of the blood with salicylates, *Proc. Soc. Exper. Biol. and Med.*, 1943, liii, 234.
14. RAPOPORT, S., WING, M. and GUEST, G. M.: Hypoprothrombinemia after salicylate administration in man and rabbits, *Proc. Soc. Exper. Biol. and Med.*, 1943, liii, 40.
15. COOMBS, F. S., WARREN, H. A., and HIGLEY, C. S.: Toxicity of salicylates, *Jr. Lab. and Clin. Med.*, 1945, xxx, 378.
16. BUTT, H. R., LEAKE, W. H., SOLLEY, R. F., GRIFFITH, G. C., HUNTINGTON, R. W., and MONTGOMERY, H.: Rheumatic fever, *Jr. Am. Med. Assoc.*, 1945, cxxviii, 1195.
17. SHAPIRO, S.: Studies on prothrombin. VI. The effect of synthetic vitamin K on the prothrombinopenia induced by salicylates in man, *Jr. Am. Med. Assoc.*, 1944, cxxv, 546.
18. KAPNICK, I., STEWART, J. D., and LYONS, C.: Plasma prothrombin and liver function during sulphonamide therapy, *New England Jr. Med.*, 1942, ccxxvii, 944.
19. CLAUSEN, F. W., and JAGER, B. V.: Relation of the plasma salicylate level to the degree of hypoprothrombinemia, *Jr. Lab. and Clin. Med.*, 1946, xxxi, 428.

PLASMOCHIN TOXICITY: ANALYSIS OF 258 CASES *

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PLASMOCHIN has had a checkered career in the rôle of an anti-malarial agent since it was first introduced into clinical medicine by Mühlens ¹ in 1926. The literature is abundant with references which approximate 400 monographs and articles, but it is not within the scope of this paper to present a historical review. Although plasmochin was initially given a trial as the sole anti-malarial drug in various types of the disease, its usage gradually became limited. It has been employed for primary attacks of malaria in combination with quinine and atabrine; in blackwater fever when sensitivity to quinine was suspected; in pregnancy complicated by malaria in order to avoid the oxytotic effects of quinine; in chronic cases in order to curb the recurrence rate; in the follow-up treatment of malaria, when sexual forms were present in the peripheral blood; and in the field for the purpose of mass suppressive treatment. In relationship to control Clark and Komp ² have reported the results of a 10 year survey in Panama concerning the administration of quinine, atabrine and plasmochin without anti-mosquito measures. Throughout these clinical reports and studies, one is able to note a variable percentage of toxic effects.

Goodman and Gilman ³ have briefly summarized the toxicity of plasmochin in their textbook of therapy. Soon after the initiation of the administration of this synthetic drug for malaria, reports on the poisonous effects were submitted. In 1927 case reports were published by Eiselsberg ⁴ and subsequently similar observations were made by Namikawa ⁵ in 1928 and Reyes ⁶ in 1929. Gastrointestinal symptoms have been noted rather early in the course of drug intake by Clark and Komp,⁷ and others. Among those who placed emphasis on cyanosis as an early toxic manifestation were Orachowatz,⁸ Chopra and Sen⁹ and Manson-Bahr.¹⁰ The question of the pigment causing the cyanotic tinge was in a controversial state. Foy and Kondi ^{11, 12} have done extensive work on this problem and concluded that methemoglobin rather than pseudo-methemoglobin was the responsible agent. The hemolytic effects of the drug have been noted by Sein,¹³ Manai ¹⁴ and others. The deleterious effects of plasmochin on the circulatory system have also been recorded,^{15, 16} and electrocardiographic studies were performed by Kawahigashi ¹⁷ in 1938. In 1943 Slatineanu and Sibi ¹⁸ presented the results of investigation of functional tests of the liver and kidney before and after atabrine therapy combined with plasmochin. Among the fatalities published were those by Decherd ¹⁹ and Blackie.²⁰

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From the Medical Service of Gorgas Hospital, Panama Canal Zone at the time Brig. Gen. Henry C. Dooling, U. S. A. was in charge. Field statistical data furnished by Col. W. C. Cox, M.C.; Lt. Col. S. J. Lerro, M.C.; and Capt. M. Vaughn, M.C.

An acute medical emergency arose as the result of plasmochin poisoning, which gave us an opportunity to study its clinical manifestations. During the month of May 1943, 401 patients were admitted to Gorgas and Margarita Hospitals, located in the Panama Canal Zone, for suspected plasmochin poisoning; 385 of this number were discharged with a substantiated diagnosis. The total number of persons who had received the drug was 4,361. Of this entire group 8.12 per cent (401) were hospitalized, another 2.01 per cent (88) showed mild reactions and were confined to quarters; so that 10.13 per cent exhibited some toxic symptoms.

The course of medicine which these individuals had received for suppressive therapy was as follows: One tablet (0.1 gm.) of atabrine was administered three times daily for five consecutive days. No medication was given on the sixth and seventh days and then for the next five days 0.01 gm. of plasmochin hydrochloride was prescribed three times daily.

The 271 cases admitted to Gorgas Hospital will be described in detail and a comparison will be made with the smaller number entering Margarita Hospital. Of the patients in Gorgas Hospital, 258 (95.2 per cent) were considered as exhibiting evidence of plasmochin toxicity.

All the patients were employed as laborers by the Panama Engineering Division and were ambulatory during the routine course of therapy. They were chiefly black and foreign white male adults in the third and fourth decades of life. No difference in reaction was noticed in the two groups. None of these patients had been immunized against yellow fever.²¹ The majority received a total of 15 tablets of atabrine (1.5 gm.) and 13 tablets of plasmochin (0.13 gm.) with a variation of the latter between six and 14 tablets. Twenty-one cases received a total of less than 10 tablets (0.10 gm.) of plasmochin, and of these, seven showed mild signs of toxicity; 12 had a moderate degree and two had severe types of reactions. The majority of the cases were admitted within a 48 hour period (May 14-15, 1943), corresponding to the last day of plasmochin intake and the day following (see table 1).

TABLE I
Relationship of Admissions to Drug Intake

Days	1-5	6-7	8	9	10	11	12	13	14	15	After
Drug—gm.	Total— 1.5	0	0.03	0.03	0.03	0.03	0.03	0	0	0	0
No. of hosp. admissions	0	0	0	0	0	8	53	145	20	24	21
	Atabrine	No med.	Plasmochin					No medication			

No definite relationship between past illnesses and the incidence or the degree of toxicity could be ascertained. A past history of malaria was obtained in 92 cases (35.65 per cent), but it did not seem to be a factor in

these cases. It contributed to the splenomegaly which was detected in many cases (24.42 per cent). No history of previous plasmochin therapy was obtained.

SYMPTOMS

The complaints following the oral administration of plasmochin, which were related to its toxicity, were in the order of frequency: Abdominal pain, dark urine (brown, red, black), anorexia, jaundice, headache, nausea, vomiting, feverishness, weakness, malaise, and backache (see table 2).

TABLE II
Analysis of Symptoms—Plasmochin Toxicity

Symptoms	Cases		Severity			Average Days After Initial Dose	
	Number	%	Mild	Mod.	Severe	Onset	Duration
Abdominal distress	178	68.99	88	71	19	4.49	3.61
Dark urine	144	55.81	42	54	48	3.88	3.99
Anorexia	116	44.96		116		4.40	4.13
Jaundice	115	44.57	48	40	27	4.15	5.40
Headache	100	38.76	58	37	5	4.75	3.37
Nausea and vomiting	87	33.73	41	31	15	4.65	2.28
Fever	64	24.81		Inestimable as a subjective sign			
Weakness, malaise	58	22.48		Undetermined			Undetermined
Backache	57	22.09	36	18	3	3.86	4.38

Less common complaints were vertigo (7.36 per cent), chest pain (5.04 per cent), diarrhea (3.87 per cent), chills (3.49 per cent), nasal congestion (2.71 per cent), cyanosis (2.33 per cent), photophobia (2.33 per cent), dysuria (1.55 per cent), palpitation (1.16 per cent), prostration (1.16 per cent), syncope (0.77 per cent), and anuria (0.77 per cent). Cyanosis was noticed by six patients but twice this number showed it upon physical examination. Likewise, the incidence of yellow sclerae noticed by the patients and their friends was less than by the examining physicians. In general, it may be stated that the onset occurred after four days of drug administration (total dosage of 0.12 gm. of plasmochin) and that the subjective symptoms lasted from three to four days. This short duration of symptoms was undoubtedly influenced by the immediate treatment the patients received.

PHYSICAL FINDINGS

The chief objective findings in the patients admitted were jaundice, general and upper abdominal tenderness, enlarged spleen and liver, cyanosis and pallor. Splenic enlargement, in many cases, was probably due to previous attacks of malaria. Most findings were of slight to a moderate degree and were detectable for a period of from two to five days (see table 3).

About one-half (56.2 per cent) of the patients had a low grade fever, which occurred early during the hospital stay and lasted but a few days. The

TABLE III
Physical Findings—Plasmochin Toxicity

Signs	Cases		Degree			Duration—Days		
	No. 258	%	Slight	Mod.	Severe	Short	Long	Average
Jaundice	138	53.49	58	50	30	1	12	4.5
Rt. U.Q. tenderness	65	25.19	37	21	7	1	10	3.5
Splenomegaly	63	24.42	43	18	2	Inestimable		
Left U.Q. tenderness	59	22.87	28	21	10	1	8	3
Gen. abd. tenderness	54	20.93	28	23	3	1	9	2.5
Hepatomegaly	46	17.82	40	5	1	Inestimable		
Cyanosis	34	13.17	28	5	1	1	6	2
Costo-vertebral tenderness	25	9.69	Undetermined			Undetermined		
Peri-umbilical tenderness	23	8.91	19	4	0	1	8	3.5
Mydriasis	8	3.10	Undetermined			Undetermined		
Shock	7	2.71	1	2	4	1	5	2.5
Nasal congestion	7	2.71	—	—	—	—	—	—
Basal râles	6	2.33	—	—	—	—	—	—
Tachycardia	5	1.94	—	—	—	—	—	—
Epigastric tenderness	2	0.77	—	—	—	—	—	—
Generalized rash	1	0.38	—	—	—	—	—	—

cases considered as seriously ill were lying in bed looking pale and cyanotic, were vomiting and complaining of abdominal distress. They also had yellow sclerae and frequently a lowered blood pressure.

LABORATORY DATA

The urine, which was collected in large bottles alongside each patient's bed, was dark in one-half of the patients on admission or during the hospital stay. The factors in producing darkness were an increase in bile pigment, the presence of oxyhemoglobin and methemoglobin and urinary concentration. About a third of the patients had urine of a red or brown-black appearance, and this served as an index of the severity of the reaction. The urine was acid on admission but after the patients had received large amounts of fluid and sodium bicarbonate, it became alkaline. No true anuria was seen after hospital admission. Renal irritation was noted in less than half of the cases and was manifested by albuminuria, hematuria or casts. Pus appeared in about a third of the cases and marked sediment and hemoglobinuria in less. Most of the abnormal urinary findings disappeared in one to three days which corresponded with the clearing of the rest of the clinical picture (see table 4). Additional laboratory studies and renal functional tests indicated no permanent renal damage.

The hemolytic anemia varied in severity and could be correlated with the intensity of the urinary findings, the elevation of the icteric index and the clinical pattern. Three-fourths of the patients had a red blood cell count below four million and about half (46.5 per cent) had a hemoglobin below 70 per cent. Fifty-six (21.7 per cent) of the cases had an erythrocyte count below two million. Many of the low counts occurred during the acute

TABLE IV
Urinary Findings—Plasmochin Toxicity

	Cases—258		Duration—Days		
	Number	%	Short	Long	Average
Dark urine	129	50	—	—	—
Red or brown-black	86	33	1	7	3
Reaction acid on admission	258	100	—	—	—
Albuminuria	104	40.31	1	7	2
Pus cells	90	34.88	—	—	2-3
Hemoglobinuria	72	27.71	—	—	1-3
Casts	52	20.15	Data not available		
Red blood cells	43	16.28	1	4	1-2
Sediment	35	13.57	—	—	1-2
Urobilin	32	12.4	Corresponded to hemolysis		

reaction after the patient was in the hospital. One red blood cell count dropped precipitously to 800,000. Likewise many (15.8 per cent) of the patients developed a hemoglobin as low as 40 per cent; the lowest was 30 per cent. The mild anemias improved in from three to four days, but the more severe lasted from 10 days to two weeks. Sternal marrow puncture in five patients showed normal regenerating normoblastic bone marrow.

A mild polymorphonuclear leukocytosis (9,000 to 12,000 per cu. mm.) occurred in most patients, though in several the white blood cell count rose as high as 20,000. No increase in lymphocytes was noted. About a fifth (22.48 per cent) of the cases showed an icteric index of over 15 units; one was as high as 175. The average duration of the elevated icteric indices was only three days. The van den Bergh test was indirect in all cases in which the icteric index was above normal.

In a limited number of the more severe cases additional laboratory data were gathered. Blood chemical tests, including glucose, cholesterol-cholesterol ester and creatinine were within normal range in eight cases. Of 162 individual studies of the blood non-protein nitrogen, elevation was noted in 12 cases. These transient rises were observed in patients exhibiting the greatest degrees of jaundice. Red blood cell fragility, Rumpel-Leeds and Donath-Landsteiner tests were normal in six cases. Kidney function tests (phenolsulfonphthalein and urea clearance) were employed in 13 cases; three were slightly reduced, but this was transitory. The renal function, as determined on the basis of the intake and output of fluids, was normal in all cases. During the peak of the illness, liver function studies (hippuric acid test) indicated some impairment in four of the 10 critically ill patients. A return to normal figures was observed after the clinical picture cleared. Of six electrocardiograms, only one revealed a transient abnormality—slight inversion of T₂ and T₃ waves. Spectroscopic examinations of the blood and urine were performed rather late in the course of the disease and therefore results cannot be considered valid. Absorption bands, indicative of methe-

moglobin and oxyhemoglobin, were detected in the urine of three of 15 cases studied, and in the blood of one of 10 cases. However, it may be assumed that methemoglobin accounted for the marked cyanosis and black urinary tint in this series.

Associated findings unrelated to the toxic syndrome were disclosed by laboratory examinations as follows: Helminthiasis 3 cases; estivo-autumnal malaria, 2 cases; latent syphilis 25 cases (serologically); infestation with *filaria ozzardi*, 1 case; and atypical pneumonia, 1 case.

The correlation of laboratory findings with the clinical picture was evident and the dark urine (urobilinuria, methemoglobinuria and hemoglobinuria), anemia, elevated icterus index, indirect van den Bergh ran parallel with the severity of the toxic process. The laboratory pattern, its transitory nature and response, were typical of an acute hemolytic process due to a toxic agent. There was no evidence of liver, kidney or bone marrow damage of a permanent nature as based on laboratory findings. Temporary renal irritation was expressed by the urinary output of albumin, casts and red blood cells in a number of specimens.

TREATMENT AND RESULTS

A therapeutic regime was immediately established for the treatment of all patients. Diagnostic procedures, which included red cell count, hemoglobin determination and urine analysis upon admission, were employed to guide special therapeutic measures. The routine treatment for each case consisted of the oral administration of thiamine chloride (15 mg. daily), ferrous sulfate (15 gr. daily), vitamin K (2,000 units daily) and sodium bicarbonate (80 gr. daily). Fluids were forced and additional sugar and fruit juices were prescribed for the first few days. Except for mild cases each patient also received 1,000 c.c. of 10 per cent glucose intravenously. If the hemoglobin was below 50 per cent (Sahli) and the red blood cells below 2.5 million or signs of impending shock were present, patients received blood transfusions, which were repeated according to their needs. The rapid influx of patients made it impossible to carry out all orders in extreme detail and the more seriously ill received the most adequate care. Some patients (27) received more than 3,000 c.c. of fluids intravenously and one received 11,000 c.c. in a five day period. Sixty patients received 92 blood transfusions as follows: 37 cases, one transfusion; 15 cases, two transfusions; 7 cases, three transfusions; 1 case, four transfusions.

✓ Blood transfusion was the treatment par excellence for the severe cases of plasmochin intoxication. Its effect was dramatic and it proved to be a life-saving measure in many cases. Even though improvement was shown there was no hesitation in repeating it. Intravenous fluids favorably influenced the clinical course of all patients and were considered an essential phase of therapy. Alkalinization of the urine was used as in black water fever which this syndrome resembles. It aids in preventing the precipitation

of hematin crystals in the renal tubules. Mild cases responded well on the ordinary routine regime.

Of the 271 cases admitted 13 were considered as exhibiting no signs of intoxication; of the rest, 136 were mild; 63 moderate; and 59 severe. The hospital stay averaged 9.76 days for all patients, although some were discharged in three days and others, severe in nature, remained for three weeks. No deaths occurred and no complications or sequelae appeared. The treatment was considered successful in each case.

The 130 patients who were admitted to Margarita Hospital, Margarita, Canal Zone, were similar to the cases we have described above in detail. One hundred and twenty-seven were diagnosed as plasmochin poisoning and 50 of this group showed hemoglobinuria. Eight patients received a total of 12 transfusions and none died. Three cases were excluded because there was no evidence of plasmochin intoxication.

Several illustrative case reports are briefly presented:

CASE REPORTS

Case 1. A 43 year old male, mestizo, laborer, employee of the Panama Canal was admitted to Gorgas Hospital on May 16, 1943 after taking the full course of suppressive treatment as outlined (0.15 gm. plasmochin). Three days prior to hospitalization he complained of abdominal distress, malaise, feeling of slight feverishness and anorexia. On the day of admission he also noted that his urine was darker than usual. Positive objective signs consisted of a slight icteric tinge of sclerae, slight cyanosis of lips and deep tenderness in the right upper quadrant.

Several daily urine specimens were negative except the first specimen which was moderately positive for urobilinogen. Daily complete blood counts were within normal limits. The icteric index on the fourth day was 15, and the van den Bergh test was indirect.

During his hospital stay he was relatively afebrile, but his pulse was slightly rapid for the first three days (90 to 100). He was placed on the routine treatment and in addition received 1,000 c.c. of 5 per cent glucose in normal saline on the first day. The rest of his course was uneventful and he was discharged as well at the end of the week. This is an example of mild plasmochin intoxication with a minimal hemolytic process, responding to a conservative regime.

Case 2. A 25 year old male, mestizo, laborer, employee of the Panama Canal was admitted to Gorgas Hospital on May 15, 1943 after an intake of 0.13 gram of plasmochin during suppressive treatment. Three days prior to hospitalization he complained of headache, nausea, feverishness, jaundice and the voiding of dark red urine. These symptoms persisted to the time of admission.

On physical examination icterus, mild cyanosis and a slightly enlarged tender liver were noted. The first specimen voided was dark red. Blood studies revealed an anemia ranging for the first few days from 1.77 to 2.66 million red blood cells with an average hemoglobin of about 60 per cent. His urine specimens revealed hemoglobinuria and urobilinuria for several days. On the fourth hospital day his icteric index was 15, non-protein nitrogen 26.9 and the van den Bergh reaction was delayed indirect.

The patient ran a low grade febrile course for the first few days. He was placed on routine therapy and in addition received a 500 c.c. blood transfusion on the second day and also 1,000 c.c. of 5 per cent glucose in normal saline intravenously. Gradual improvement was noted and he was discharged as well on the tenth day. This is an

example of a moderately severe case of plasmochin intoxication with a satisfactory response to routine therapy and a blood transfusion.

Case 3. A 35 year old, black, male laborer, employee of the Panama Canal, was admitted to Gorgas Hospital on May 15, 1943 after an intake of 0.12 gram of plasmochin during suppressive treatment. Two days prior to admission he complained of abdominal distress, malaise, headache, nausea, vomiting, anorexia, jaundice and the voiding of very dark urine.

Physical examination revealed an acutely ill individual in mild shock with a small rapid pulse, exhibiting signs of marked jaundice and moderate cyanosis. General abdominal tenderness was elicited on deep pressure and he had moderate mydriasis.

The red cell count was 1.9 million red cells on admission and for several days was under 2.5 million. The hemoglobin was 50 per cent. The initial white cell count was 18,000 with a polymorphonuclear trend. The urine had a blackish tint on the first day and was dark red on the second day. Albuminuria, methemoglobinuria and hemoglobinuria were detected for several days. Kidney function tests were sub-normal (phenolsulfonphthalein was 20 per cent) on fourth day, but on the eighth day the urea clearance was normal. Blood examinations on fourth day revealed an elevated non-protein nitrogen (44.6 mg.) and normal blood sugar (80 mg.). The initial icteric index was 42 units. A sternal puncture indicated an active bone marrow response to hemolysis. Spectroscopic examination of the blood revealed the presence of methemoglobin. Electrocardiographic studies showed slight inversion of T_2 and T_3 waves.

The patient had a temperature of 100 to 102° F. during the first week and was seriously ill. During this period he received three blood transfusions and three intravenous infusions of 5 per cent glucose in normal saline. He gradually felt better, became afebrile, the urine analysis reverted to normal and his red cell count rose to 3.15 million and 72 per cent hemoglobin. He was discharged at the end of two weeks. This is an example of a case of severe plasmochin intoxication with severe hemolysis and methemoglobinuria and the rare findings of shock, mydriasis, renal irritation and toxic myocarditis (see figure 1). Energetic measures were necessary in the therapy of this case.

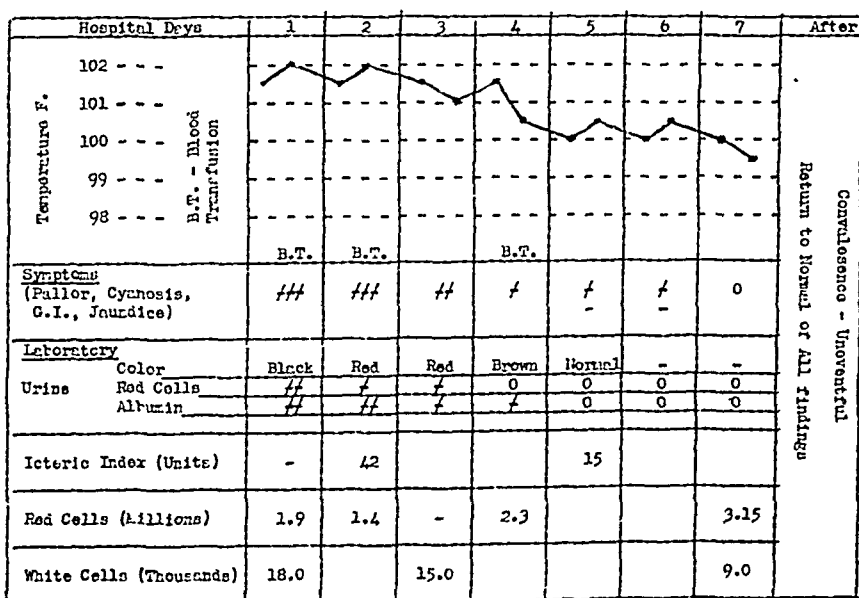


FIG. 1. Composite chart of case 3 (severe plasmochin intoxication).

COMMENT

On the basis of the data in this report, it is evident that plasmochin is a dangerous drug and due caution must be exercised in its administration. It has a limited use and at present it is employed at Gorgas Hospital in selected recurrent cases of malaria and all cases which persistently reveal the sexual forms of the parasite in the peripheral blood, after an adequate course of another anti-malarial drug (atabrine or quinine) has been prescribed. It is recommended that the dosage of plasmochin be modified because of the small margin of safety and the individual sensitivity occasionally encountered. At present the dosage at Gorgas Hospital has been reduced to 0.01 gm. twice daily for a period of three days. It is also felt that plasmochin should not be used in the field, but as a rule in a hospital, where more careful observation by the physician is possible. When early signs of toxicity appear, the drug must be discontinued. If jaundice, pallor or impending shock occur, then energetic measures of therapy as outlined (blood transfusion, intravenous fluids, etc.) should be instituted. Laboratory studies, particularly daily blood counts and urine analysis, are important in the diagnosis, treatment and follow-up of each case.

The rôle of atabrine in the introduction or accentuation of toxic symptoms cannot be fully evaluated in this series.

CONCLUSION

Of 4,361 laborers who were placed on a suppressive ambulatory routine for malaria (five day course of 1.5 gm. atabrine followed by two days of no medication and then a five day course of 0.15 gm. plasmochin hydrochloride), 489 cases (10.13 per cent) developed toxic manifestations of plasmochin poisoning. The individual syndrome varied in severity but the more seriously ill presented the typical clinical and laboratory pattern of acute intravascular hemolysis. All cases recovered upon a therapeutic regime which included alkalinization of the urine, intravenous fluids and blood transfusions, and no permanent effects were noted. Plasmochin is a drug which presents a potential danger to the patient and therefore the reduction in dosage and the careful observation of patients receiving the drug are recommended.

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BIBLIOGRAPHY

1. MÜHLENS, P.: Die Behandlung der natürlichen menschlichen Malaria-infektion mit Plasmochin, *Naturwissenschaften*, 1926, xiv, 1162-1166.
2. CLARK, H. C., and KOMP, W.: A summary of ten years of observation on malaria in Panama with reference to control with quinine, atabrine, and plasmochin, without anti-mosquito measures, *Human Malaria*, Pub. No. 15, Am. Assoc. Adv. Sci., Washington, D. C., 1942, 273-284.

3. GOODMAN, L., and GILMAN, A.: The pharmacological basis of therapeutics, The Mac-Millan Co., N. Y., 1941, page 917.
4. EISELSBERG, K. P.: Poisoning (plasmochin); 2 cases, *Wien. klin. Wchnschr.*, 1927, xl, 525.
5. NAMIKAWA, H.: Symptoms of poisoning in the treatment of malaria, *Taiwan Igakkai Zasshi*, 1928, cclxxxiv, 75.
6. REYES, F.: Toxicity (plasmochin) cases, *Rev. de clin. Med.*, 1929, vii, 338.
7. See (2), page 283.
8. ORACHOWATZ, D.: Toxicity, cyanosis induced by plasmochin treatment of malaria, *Arch. f. Schiffs.-u. Tropen. Hyg.*, 1928, xxxii, 119-121.
9. CHOPRA, R. N., and SEN, B.: Cyanosis after plasmochin, *Indian Med. Gaz.*, 1933, lxviii, 26-27.
10. MANSON-BAHR, P. H.: Further observations on plasmochin and plasmochin-compound, *Lancet*, 1928, ccxiv, 25.
11. FOY, H., and KONDI, A.: Spectrographic analysis of pigments in serum and urine of blackwater fever, *Trans. Roy. Soc. Trop. Med. and Hyg.*, 1938, xxxii, 49-65.
12. FOY, H., and KONDI, A.: Note on intracorpuseular methemoglobin in plasmochin toxicity, *Ann. Trop. Med.*, 1938, xxxii, 249-256.
13. SEIN, M.: Case of hemoglobinuria caused by plasmochin, taken as prophylactic against malaria, *Indian Med. Gaz.*, 1937, lxxii, 86-87.
14. MANAI, A.: Toxicity, causing hemolytic jaundice, *Policlinico (sez. prot.)*, 1929, xxxvi, 1215-1217.
15. EICHOLTZ, Z.: Circulatory disturbances caused by plasmochin and atabrine, *Klin. Wchnschr.*, 1935, xiv, 716-718.
16. HECHT, G.: Circulatory disturbances caused by plasmochin and atabrine, *Klin. Wchnschr.*, 1935, xiv, 714-716.
17. KAWAHIGASHI, K.: Toxicity, electrocardiogram in plasmochin cyanosis, *Taiwan Igakkai Zasshi*, 1938, xxxvii, 554.
18. SLATINEANU, A., and SIBI, R.: Functional exploration of liver and kidney before and after therapy with atabrine alone or combined with plasmochin or quinine, *Arch. Roumaines de path. expér. et de microbiol.*, 1943, vii, 529-543.
19. DECHERD, G. M., JR.: Fatality after atabrine-plasmochin treatment of malaria (case), *Jr. Trop. Med.*, 1937, xl, 90-91.
20. BLACKIE, W. K.: Fatal case of poisoning (plasmochin), *South African Med. Jr.*, 1935, ix, 147-148.
21. WEST, J. B., and HENDERSON: Plasmochin intoxication, *Bull. U. S. Army Med. Dept.*—number 82. November 1944, p. 87.

INFECTIOUS MONONUCLEOSIS: REPORT OF AN EPIDEMIC IN AN ARMY POST*

PART I

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EPIDEMICS of infectious mononucleosis¹ are not infrequent, especially where groups of young individuals live in close proximity. Outbreaks in colleges and schools have been the classical examples of such epidemics. They have also occurred in military installations. The first epidemic in this country was described by West^{1 (k)} in 1896.

The post, in the period during which the epidemic took place, was of diverse and changing composition. In the main, it consisted of the station complement and a large number of battalions in training. The former and smaller component consisted of individuals who usually had had from one to several years of service and its composition changed but slowly. The battalions, on the other hand, arrived and departed at irregular intervals, varied in strength between 700 and 1000 men, were mostly recent inductees and remained on the post usually for a period of four to six months.

Before embarking on a description of the epidemic, the diagnostic criteria we used must be stated. This is necessary not only because of the protean manifestations of the disease and its unknown etiology, but because of the large number of cases with insidious onset and mild symptoms or with no clinical manifestations whatsoever. The latter were admitted for some totally unrelated condition. That there can be many such cases during an epidemic, has been amply confirmed by Halcrow and co-workers² in a recent outbreak of the disease in an E.M.S. hospital in Scotland. Of the 298 individuals whom they examined, a group composed of both patients and nursing staff, 97.9 per cent showed evidence of the disease. Only 125 of these were clinical cases, whereas 165 had blood and serological changes but no clinical manifestations. What was even more remarkable was the demonstration of many cases in the adjacent town and a few in two towns situated 13 and 20 miles from the hospital. It is interesting that Baldrige,³ as early as 1926, asserted that sporadic cases are only the more marked instances of a small epidemic in which many of the cases are so mild as to escape notice.

Both in the absence of clinical manifestations and as confirmation of the suspect clinical syndrome, the diagnosis is based on the presence of "leukocytoid" lymphocytes in the peripheral blood, a mononucleosis, a positive

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Major Jesse Schapiro supervised the laboratory procedures. Major Louis Johnson assisted in the preparation of the dermatologic section.

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heterophile antibody agglutination test, or a combination of these three. The application of these criteria to the large number of cases seen in an epidemic such as we are describing presents certain difficulties.

A number of workers have denied that "leukocytoid" lymphocytes are pathognomonic of infectious mononucleosis. Baldridge et al.³ found varying percentages of abnormal lymphocytes in many infections associated with lymph node involvement. In a number of cases of upper respiratory infections, such as acute pharyngitis and acute sinusitis, Warren⁴ reported that many of them showed from 1 per cent to 10 per cent of cells characteristic of infectious mononucleosis. Fifteen heterophile antibody agglutination tests were performed in these cases and all were negative. He admitted, however, that serial blood counts and heterophile antibody agglutinations were not complete. Randolph and Gibson⁵ studied 24 allergic students, nurses and hospital personnel whose major complaint was fatigue or weakness and found atypical lymphocytes present in a range from 2 to 27 per cent. One was known to have had infectious mononucleosis two years earlier and eight had or had had cervical gland enlargement. A heterophile antibody determination was performed in 22 and the highest titer was 1:32. In a continuation of these studies in a group of 140 student nurses, Gibson and Hettig⁶ reported that atypical lymphocytes varied between none and 22 per cent. On the basis of the single blood count performed, however, the number of such lymphocytes bore no relationship to a past history of allergic disease. Infectious mononucleosis had been previously diagnosed in two because of a positive heterophile antibody determination. This test, unfortunately, was not a part of the study. Although the authors discount the possibility that they were dealing with an epidemic of infectious mononucleosis or with cases in the recovery phase of this disease, no convincing evidence is presented. No Davidsohn absorption tests were performed. The occurrence of seronegative cases and the frequent, rapid disappearance of elevated heterophile titers during convalescence are not taken into consideration. The reported cases were in a group in whom infectious mononucleosis is common and it is known that atypical lymphocytes can persist for months and even for years after an attack. They have been reported as long as 7 and 10 years later.^{3,7} Finally, atypical lymphocytes are apparently common in infectious hepatitis. In 1923, Jones and Minot⁸ reported 26 sporadic cases in whom such cells reached 50 per cent during the height of the lymphocytosis. No heterophile antibody determinations were performed. Recently, Barker, Capps and Allen⁹ found 5 to 20 per cent and occasionally as high as 60 per cent of these cells in an epidemic of infectious hepatitis. Heterophile antibodies were consistently absent on repeated examinations.

A mononucleosis at some stage of the disease has been considered the essential sign in infectious mononucleosis by Bernstein.¹⁰ He, however, quotes Chevallier to the effect that in some instances the mononucleosis may be so slight that the diagnosis depends only on the presence of abnormal cells. His conclusion, moreover, is based on sporadic cases which are usually severe

enough to warrant prolonged observation and frequent blood counts. In addition, there is a general agreement that the mononucleosis is much higher in sporadic cases than in those seen in an epidemic.^{1 (c), 1 (d), 3, 11}

Although the Paul-Bunnell test¹² has been a great advance in the diagnosis of infectious mononucleosis, it has many limitations when applied to the epidemic disease. The variability in the time of appearance of the maximum titer and the occasional rapid disappearance of elevated values^{10, 13, 14, 15} are great disadvantages where repeated tests are not feasible or where large numbers of asymptomatic cases are concerned. The number of sero-negative cases is not inconsiderable. In the sporadic form, the percentage of positive tests has varied between 43 per cent and 100 per cent.¹³ The variation has depended to some extent upon the frequency with which the test has been performed in the individual cases, the technic employed and the titer that was considered as a positive test. More important, however, has been the number of cases the author has excluded merely because the test was negative.^{13, 16, 17} Such a procedure has even been recommended.¹⁸ On the other hand, the test is not specific as not only have rare false-positives been reported^{19, 20, 21} but normal sera can and often do contain sheep-cell agglutinins. Excluding serum sickness and converting the values into final dilutions, the maximum titers that have been reported in the literature are shown in table 1. Although titers above 1:64 and 1:80 occur in only a very small number of controls, the fact that they do occur is more important than the actual percentage where clinical manifestations are completely absent or mimic a great variety of other illnesses. The Davidsohn absorption test³⁰ is undoubtedly of greater usefulness under such circumstances. This test, however, is more complicated and places a heavy burden upon a laboratory staff already overtaxed with other duties, particularly when large numbers of patients are involved. The introduction of modifications in technic which shorten the test^{13, 31} do not decrease its complexity. Moreover, the absorption test as performed in our laboratory did not give uniform results. This was true of both the guinea-pig and the beef red cell suspensions and will be more fully discussed later.

TABLE I
Maximum Titer of Sheep-Cell Agglutinins in Control Series

Author	Number of cases tested	Maximum titers	Author	Number of cases tested	Maximum titers
Barrett ¹⁶	100	1:20	Bunnell ²⁶	2015	1:128
Davidsohn ²²	217	1:56	Butt and Foord ²⁷	436	1:128
Smeall ²³	765	1:64	Stuart ²⁸	300	1:320
Shaw and Macgregor ²⁴	136	1:64	Beeukes ²¹	100	1:516
Bernstein ²⁵	300	1:80	Demanche ²⁹	147	1:896

In all suspected cases in this epidemic, several blood counts and at least one heterophile antibody agglutination test were performed, but no systematic attempt was made to determine the maximum percentage of "leuko-

cytoid" lymphocytes, the maximum mononucleosis or the highest heterophile antibody titer attainable. Davidsohn absorption tests were done in a number of typical cases throughout the period of study merely to confirm the fact that we were dealing with an epidemic of infectious mononucleosis. They were also performed in doubtful cases and in those who presented a German measles or scarlatiniform rash, jaundice or pneumonia. More extensive studies were undertaken only in those patients who required prolonged hospitalization, either because of their admitting illness or because of the severity of the infectious mononucleosis. The ordinary cases with clinical manifestations of the disease were usually symptom-free after four to five days of hospitalization and anxious to return to duty. It was not deemed advisable to interfere with their training program solely for the purpose of making further blood studies.

For the purposes of this report, we have arbitrarily excluded all cases who had less than 10 per cent "leukocytoid" lymphocytes of the total white blood cell count, unless the heterophile antibody agglutination titer was 1:224 or above or was positive with the Davidsohn test. We realize that many cases of infectious mononucleosis were excluded by these criteria, either because of insufficient blood studies or because they were admitted to the hospital in a late convalescent stage. During the height of the epidemic, practically every patient in the hospital showed varying percentages of abnormal lymphocytes in their blood smears. As only those cases actually seen at the hospital form the basis of this report, it is evident that there must have been large numbers without clinical manifestations or with such mild symptoms that they were never hospitalized. Many of the latter either stayed on duty or were confined to quarters for a day or two.

This study includes only the 556 cases admitted or examined at the hospital between January 1, 1943, and February 29, 1944. Up to July, 1944 an additional 131 cases were admitted but have not been tabulated, as the essential facts and conclusions would not have been altered by their inclusion.

DISTRIBUTION

A. Monthly Incidence. The outbreak began in August 1943, but sporadic cases were recognized prior to this date. In the preceding seven months there were 11 cases diagnosed as infectious mononucleosis.

The monthly incidence is shown in table 2. It will be noted that the admission rate rose rapidly to its peak in October and November 1943 and

TABLE II
Distribution by Month of Admission

Month	Number of cases	Month	Number of cases
Jan. to Aug. 1943	11	November 1943	147
August 1943	18	December 1943	104
September 1943	46	January 1944	59
October 1943	139	February 1944	34

then declined more slowly. Small numbers of cases were admitted in the succeeding months of 1944 not covered by this report. The numbers in these months were as follows: March, 40; April, 34; May, 39; June, 18.

Most epidemics have occurred in the spring and fall.¹⁰ However, the epidemic described by Halcrow et al.² in England, which had many similarities to our own, began in August. Although sporadic cases are more frequent in the winter months, no month is spared.^{10, 32, 33} June is the hottest month of the year in this region and it stays warm until October. Although the height of the epidemic was in the fall, it began in a very hot August and cases were admitted as late as the following June.

B. Age. The cases which we are reporting consist of military personnel exclusively and therefore belong to a limited age group. The distribution by age of the epidemic cases and of the army as a whole are shown in table 3. The latter is a compilation based on personnel surveys as of December 31, 1943 and June 30, 1944.

TABLE III
Age Distribution of Epidemic Cases and of Army as of December 31, 1943 and June 30, 1944

Age	Epidemic Cases		Army December 31, 1943	Army June 30, 1944
	Number of cases	Percentage	Percentage	Percentage
18	57	10.2	3.6	0.7
19	59	10.6	6.9	4.0
20	58	10.4	7.6	7.1
21	35	6.2	8.4	7.3
22	37	6.6	8.7	7.8
23	34	6.1	7.9	8.4
24	34	6.1	7.7	7.8
25	31	5.5	7.1	7.5
26	33	5.9	5.4	7.0
27	15	2.6	5.0	5.7
28	22	3.9	4.4	5.0
29	22	3.9	4.0	4.4
30	18	3.2	3.4	4.0
31	19	3.4	3.1	3.5
32	19	3.4	2.6	3.0
33	13	2.3	2.4	2.7
34	13	2.3	2.1	2.4
35	12	2.1	2.0	2.2
36	7	1.2	1.7	2.0
37	8	1.4	1.5	1.8
38	8	1.4	1.0	1.5
39	0			
40	1			
41	0			
42	1			
43	1	0.7	2.5	2.1
44	0			
45	0			
46	0			
47	1			

The ages of the patients ranged between 18 and 47 years. From the table, it is evident that there was a greater frequency of the disease at age

18 to 20 years inclusive when compared to their percentage strength in the army. This was very marked in the 18 year old group, the frequency being 3 to 14 times as great. From ages 21 to 25 years inclusive, the case rate was somewhat lower and from 26 to 38 years inclusive, it closely approximated the percentage age composition of the army. After 38 years, there was only an occasional case and a much lower incidence than the expected rate.

All authors have stressed the fact that infectious mononucleosis is largely a disease of children and young adults.¹⁰ As a classical example of this, the outbreak at the Lawrenceville School^{1 (6)} is often cited. Adults, however, are not immune. In an epidemic in the Falkland Islands,³⁴ 10 per cent of the cases were between 45 and 65 years of age and in the one described by Halcrow et al.,² most of the patients were between 20 and 45 years of age. Two patients were aged 64 and 84 years respectively.

Analysis of the age incidence in the epidemic indicates that the younger individuals, especially those 18 years of age, are more susceptible to the disease. It also indicates that the so-called relative immunity of adults, at least until age 39 years is reached, does not obtain where a group lives closely together and where the opportunities for contact are favorable.

C. Sex. There were four females in this series, or 0.7 per cent of the total number. This is proportional to their representation on the post, as hospital admissions were limited to nurses and WACs, and did not include dependents.

D. Color. Infectious mononucleosis in the negro is supposed to be a rarity. Bernstein,¹⁰ in 1940, could find but a single case³⁵ reported in the literature up to that time.

Since then, there have been 15 additional cases. In 1941, Werlin, Dolgopol and Stern³⁶ reported four cases and noted that all were seen in one month and from the same district of New York City. Ray and Cecil,³⁷ in 1944 reported three cases, one of which was complicated by sickle cell anemia and in the same year, Johnson³⁸ reported two cases in children. Recently, Blain and Vonder Heide³⁹ reported six cases, two of which, however, were doubtful by our criteria as no atypical lymphocytes were noted.

There were 49 negroes in this series or 8.7 per cent of the total number of cases. Except for the month of August, 1943, when the outbreak started and during which the case rate was the lowest, this percentage was considerably higher than the percentage colored strength on the post. For the last five months of 1943 and the first two months of 1944, the period covered by this report, the percentage colored strength was as follows: August, 10.2 per cent; September, 3.6 per cent; October, 3.2 per cent; November, 5.8 per cent; December, 5.0 per cent; January, 3.2 per cent; February, 2.9 per cent. The average for these seven months was 4.8 per cent or about half the actual incidence.

These statistics indicate that infectious mononucleosis is not a rarity among the negro, but that, on the contrary, he apparently has a greater sus-

ceptibility to the disease. They support Bernstein's¹⁰ contention that the paucity of reported cases in the negro is due to the fact that members of this race with minor illnesses are not hospitalized.

E. Race. We have encountered the disease in all races including those of Hindu and Chinese extraction. Italian prisoners of war were represented by 11 cases. There were 24 Jews in this series or 4.3 per cent of the total. It was our impression that this percentage was also approximately their strength on the post and that they did not exhibit any increased susceptibility to the disease.

F. Organizations. Every outfit was represented by one or more cases. Twenty-one organizations contributed 10 or more cases. The Station Hospital personnel with 35 cases was the largest group.

Bernstein¹⁰ is of the opinion that the frequency of infectious mononucleosis among individuals working about a hospital has been overemphasized. He feels that these individuals are promptly hospitalized for the treatment of even trifling illnesses and are, therefore, correctly diagnosed.

This situation, however, did not obtain in the post. Minor illnesses among line troops were more frequently hospitalized than among service troops. Because of the arduous physical exertion required of the former, the unit medical officer recommended hospitalization in the vast majority of cases if there was a significant temperature elevation.

We must also emphasize the fact that no epidemiological survey of the hospital personnel was undertaken and that the discovery of the disease depended upon the same factors as in the other troops. It would, therefore, favor the belief that the epidemic disease is actually more frequent in hospital personnel, presumably due to the increased opportunity of contact with persons afflicted with the disease.

CLINICAL PICTURE

1. Clinical Types. In a disease as protean in its manifestations as infectious mononucleosis, we have found it both interesting and instructive to classify the cases in this epidemic into clinical types. This, at times, was not a simple matter as many cases did not readily fit into any arbitrary classification. In large numbers, manifestations of several types were present either simultaneously or at various times during the course of the illness.

We have classified the cases on the basis of the outstanding clinical feature, such as the presence of jaundice, skin eruptions, meningitic signs, pneumonia, etc. The importance of such a classification in the differential diagnosis is apparent. In table 4 are listed the various clinical syndromes we have encountered and their frequency.

2. Mode of Onset. In contrast to sporadic cases, the onset in the majority was acute, with a chill or chilly feelings and fever. In a few of the anginose, but especially in the icteric and lymphoglandular types, there was a period varying from several days to two weeks, in which there were vague constitutional symptoms such as malaise, fatigability, headache and anorexia,

TABLE IV
Distribution by Clinical Types.

Type	Number of cases	Percentage	Type	Number of cases	Percentage
Anginose	256	47	Pulmonary	30	5
Insidious	112	20	Abdominal	12	2
Eruptive	92	16	Lympho- glandular	11	2
Icteric	34	6	Meningitic	9	2

with or without a mild sore throat. The insidious cases were discovered by routine blood count in soldiers admitted to the hospital for a variety of other conditions. Even in the acute cases, the date of admission was rarely the day of onset of the disease, as most of the soldiers attempted to remain on duty without going on sick call or were treated in the dispensaries by their unit surgeons. Some were referred to the Skin Clinic because of the discovery of an eruption, while others developed the disease while under observation in the hospital. In two cases, the finding of a positive blood Kahn reaction led to other blood studies.

3. *Initial Symptoms.* From the classification into types, the initial symptoms and their frequency can be inferred. In the anginose type, the patients complained of chills or chilly sensations, fever, sore throat, malaise, headache, generalized aches and pains, sweats, and anorexia. Depending upon the severity of the sore throat and upon the extent of involvement of the respiratory tract, a non-productive cough, coryza, pains in the anterior part of the chest, painful deglutition and hoarseness were not infrequent. Dizziness, nausea, and vomiting occurred but were not common. A few cases were ushered in by an epistaxis.

The pneumonic type was merely a variant of the anginose type, differing from it in the severity of the cough and the presence of pain in the chest. When this syndrome was accompanied by a polymorphous eruption, the patient appeared seriously ill.

Although the insidious type had no clinical manifestations of the disease and the patients were admitted for unrelated conditions, careful questioning frequently elicited a history of a mild sore throat one or more weeks previously. A mild cervical or generalized lymphadenopathy was practically always present and at times the spleen was palpable.

In the eruptive form, although the mode of onset was similar to the anginose type, the patient exhibited skin lesions on admission or developed them shortly thereafter. In a few cases the upper respiratory symptoms were mild and the patient sought admission solely because of the eruption.

The initial symptoms in the icteric type were variable, depending on the presence or severity of the throat involvement. Where the sore throat was absent or mild, the symptoms were less violent, the patients entered the hospital at a much later date and the prominent complaints were malaise, anorexia, nausea, vomiting and epigastric distress, followed by jaundice.

Fever was absent or mild. In those with a moderate or severe sore throat, fever, chills and headache were present in addition to the above symptoms.

Upper respiratory symptoms were absent or mild in the abdominal type and the presenting symptoms were pain in the abdomen, nausea and vomiting. The pain was situated in the right lower quadrant, the right upper quadrant or the epigastrium.

In the lymphoglandular type, the sore throat was mild or had disappeared and the patient's only complaint was painful swollen glands. Although the lymphadenopathy was invariably generalized, the most prominent glands and the ones which were the most painful were always the cervical lymph nodes, except in one instance, where the pain was confined to the inguinal region. Lesser pains were not infrequently complained of in the axillae, the groins, or both.

In the meningitic type, the anginose symptoms were moderate or severe but in addition, there were severe frontal headache and pain and stiffness of the neck. These were occasionally accompanied by vomiting.

Upper respiratory symptoms were absent in the malarial form, the complaints being daily chills, fever, headache, malaise and sweats.

4. Duration of Attack. It is very difficult to arrive at any satisfactory conclusion concerning the duration of the attack in the cases in this series. Neither the duration of clinical manifestations nor the duration of fever applied to all patients. The insidious cases exhibited no clinical manifestations at the time of admission. On the other hand, there were 50 cases who presented such varied clinical manifestations as icterus, mild angina, stomatitis or skin eruptions and yet were afebrile on admission. Some of both groups, however, acknowledged a recent, mild sore throat while many stated that they had had chills or fever or both at some time prior to admission. It is of interest that in six of this afebrile group a relapse occurred which was accompanied by fever.

Another factor was the great variation in the period between the onset of the disease and admission to the hospital. This interval ranged from a few hours to 25 days in 417 cases in which the data concerning this period were reliable. The average number of days of illness prior to hospitalization for this entire group was three. In 19 cases the onset of the disease occurred in the hospital while under observation for some other, unrelated condition.

There were 377 cases who exhibited an elevated temperature with the acute phase of the disease. The duration of the febrile course in the hospital ranged from one to 35 days. The elevation lasted for only one day in 97 of these cases. Arranged according to weeks of temperature, the duration was as follows: One week or less, 89 per cent; one to two weeks, 9 per cent; two to three weeks, 1 per cent; three to four weeks, 1 per cent. This is in marked contrast to the sporadic cases reported in the literature.¹⁰ These figures do not include the prolonged low-grade fever in convalescence or the relapses. There were 18 cases who exhibited a low-grade fever for a period

varying between two weeks and three months. As this manifestation was disregarded in judging the soldier's fitness for duty, the actual persistence of this phenomenon cannot be given. Relapses will be discussed elsewhere.

In contrast again to sporadic cases,¹⁰ the peak of the temperature in the vast majority of instances occurred on the first or second day. The temperature peaks in this series are shown in table 5. The insidious cases accounted for the large percentage with a peak of less than 99° F. The highest temperature recorded in this series was 105.6° F.

TABLE V
Peaks of Temperature

Temperature	Percentage of cases	Temperature	Percentage of cases
98° to 99° F.	26	102° to 103° F.	14
99° to 100° F.	15	103° to 104° F.	12
100° to 101° F.	12	104° to 105° F.	6
101° to 102° F.	14	105° to 106° F.	1

5. *Pulse.* In general, the pulse rate paralleled the temperature. There were a few cases with temperatures over 102° and less frequently with temperatures over 103° whose pulse rates were only 80 to 88. What was especially striking, however, was the great frequency of bradycardia in convalescence.

6. *Respiratory System.* Subjectively, sore throat was the commonest complaint. Although angina was the prominent objective feature in only 47 per cent of the cases as shown in table 4, it must be emphasized that the majority of those belonging to the other types exhibited evidence of involvement of the pharynx at some time during their hospital stay so that signs of throat involvement were present in 73 per cent of the patients. This percentage would have been much greater, if there were added to it the insidious cases with a history of sore throat and those acute cases whose sore throat had subsided by the time they entered the hospital. In some patients, especially those belonging to the icteric type, the sore throat appeared later in the course of the disease and in still others, throat involvement occurred with a relapse.

There were five types of throat infection: diffuse injection of the pharynx, tonsils or both of varying degrees (68 per cent); follicular tonsillitis or pharyngitis (18 per cent); ulcerative tonsillitis or pharyngitis (9 per cent); membranous tonsillitis or pharyngitis (3 per cent); stomatitis (2 per cent). No case developed a peritonsillar abscess. The stomatitis was of the aphthous variety and was very diffusely distributed, involving the pharynx, tonsils, soft palate, buccal mucous membranes, gums, tongue and even lips. In one confusing case with marked ulcerative stomatitis, a bullous eruption appeared on the palms and soles. Several others were complicated by a polymorphous eruption.

The soft palate was very frequently involved in the various types of throat infection and in a few cases exhibited scattered petechiae. A gingivitis was extremely common. It was usually mild and consisted of puffiness, redness and easy bleeding of the gums. In 52 cases, it was severe and ulcerative in character. Epistaxis was rare, occurring in only four cases. When it did occur, however, it was of moderate severity, ushered in the illness and was the only finding on admission. Herpes labialis was rare, being mentioned in only six cases.

Although cough was a common symptom, pulmonary findings were present in only 30 cases. The initial symptoms did not differ from the anginose type except for the severity of the cough and the more frequent complaint of pain in the chest. The cough was of the spasmodic type and was frequently described as pertussis-like. Audible wheezing was occasionally present. It was only slightly productive of thick, tenacious sputum. In only one case was it blood-tinged. The pain in the chest was usually sternal but occasionally referred to either lung. Numerous diffuse sibilant and sonorous râles, inspiratory and expiratory, were heard without change in the percussion note or breath sounds. In a few cases, fine râles in addition to the rhonchi were audible over a portion of the lung. In 14 of these cases, a pneumonitis was demonstrated by roentgen-ray. The roentgen-rays were not always positive on admission but became so two or three days later and in one instance, they became positive with a relapse on the eighth hospital day following three days of normal temperature.

The highest temperature in this group varied between 99.2° and 105° F., and the febrile course varied between one and three days in all except two cases. In these two, it lasted six days. The latter were the only ones who appeared very ill and were also the patients with the highest temperature. One of these, whose temperature rose to 104.8° , was taken ill, two days before admission, with chilliness, fever, sore throat, cough, malaise, generalized aching, nausea and vomiting. He showed a severe, ulcerative stomatitis, involving pharynx, tonsils, soft palate, buccal mucous membranes and gums. There were pronounced asthmatic wheezing, moderate cyanosis, diffuse, sibilant and sonorous inspiratory and expiratory râles and moderate fine moist râles over the right lung posteriorly. Roentgen-rays revealed a mottled density involving the entire right lung and the first, second and third left interspaces. The day after admission, he developed a generalized polymorphous eruption, papular, nodular and vesicular in character. The other case, whose temperature rose to 105° , had been ill for five days prior to admission with the usual symptoms. Besides a moderate pharyngitis and diffuse rhonchi over both lungs, he also exhibited a generalized polymorphous eruption on entrance into the hospital. His roentgen-ray revealed a diffuse hazing of the upper two-thirds of the right lung except for the apex.

The rest of the cases were all mild and indeed, the finding of a pneumonia and its extent were always a surprise. In one remarkable example, a WAC who had been ill for five days with chilliness, sore throat, fever and

cough, the highest temperature was 99.2° , which continued for three days. The roentgen-rays of the chest showed a pneumonitis involving the entire left lung field except the apex and costophrenic angle. Another, who had been ill for only one day and whose roentgen-ray showed a pneumonitis involving the medial third of the lower right lung field, had no temperature on admission. His highest temperature was 99.2° on the second hospital day.

Some type of angina was present in all. Herpes labialis was present in four cases. The laboratory findings were interesting. The sputum did not contain pneumococci or other significant organisms on typing or culture. Vincent's organisms were found on throat smears. Blood cultures were sterile. The blood counts shortly after admission were variable. The white blood cells varied from 4,600 to 32,000 and the neutrophils from 48 to 86 per cent. The majority showed a normal or elevated count with an increased number of neutrophils. The others showed a normal white blood cell count or a leukopenia with a moderate lymphocytosis. In from several days to a week, there was a shift to a leukopenia and a mononucleosis in the first group and an increased mononucleosis in the second. The lowest count in this period was 4,000 and the largest percentage of mononuclears was 67 per cent. This was in keeping with the hematological findings in the anginose group in general.

The roentgenological appearance of the lesions (figures 1, 2, 3, 4, 5) were indistinguishable from those described in atypical pneumonia and consisted of a haziness or mottling through which the ribs could be seen. The right lower lobe alone was involved in five cases, the left lower lobe in two, the right middle lobe in two and the right upper lobe in one case. In three cases, more than one lobe was involved. Clearing of the roentgen-ray findings took place very rapidly.

In the remaining 16 cases, the roentgen-rays were negative in all but two. In one patient, who coughed up bloody mucus, a roentgen-ray shortly after admission revealed a haziness in the left lower lobe suggestive of an early pneumonitis. However, two days later, another roentgen-ray was reported as negative. In the other, the initial roentgen-ray was reported as showing changes in both lower lung fields suggestive of acute bronchial irritation. Another film taken four days later was negative.

The literature contains many references to the similarity between the cough in these cases and that in pertussis and to the likelihood that enlarged intrathoracic glands are the cause in both. We have been unable to demonstrate enlarged mediastinal glands in any of this group or in 23 additional patients in whom chest roentgen-rays were taken because of the severity or character of the cough. Râles were not audible in the latter group.

Whether the acute bronchitis or actual pneumonitis, present in 2.9 and 2.5 per cent of the patients respectively, was a complication due to secondary invaders or part of the disease process itself, cannot be stated with certainty. There were many striking similarities between the type of pneumonitis we

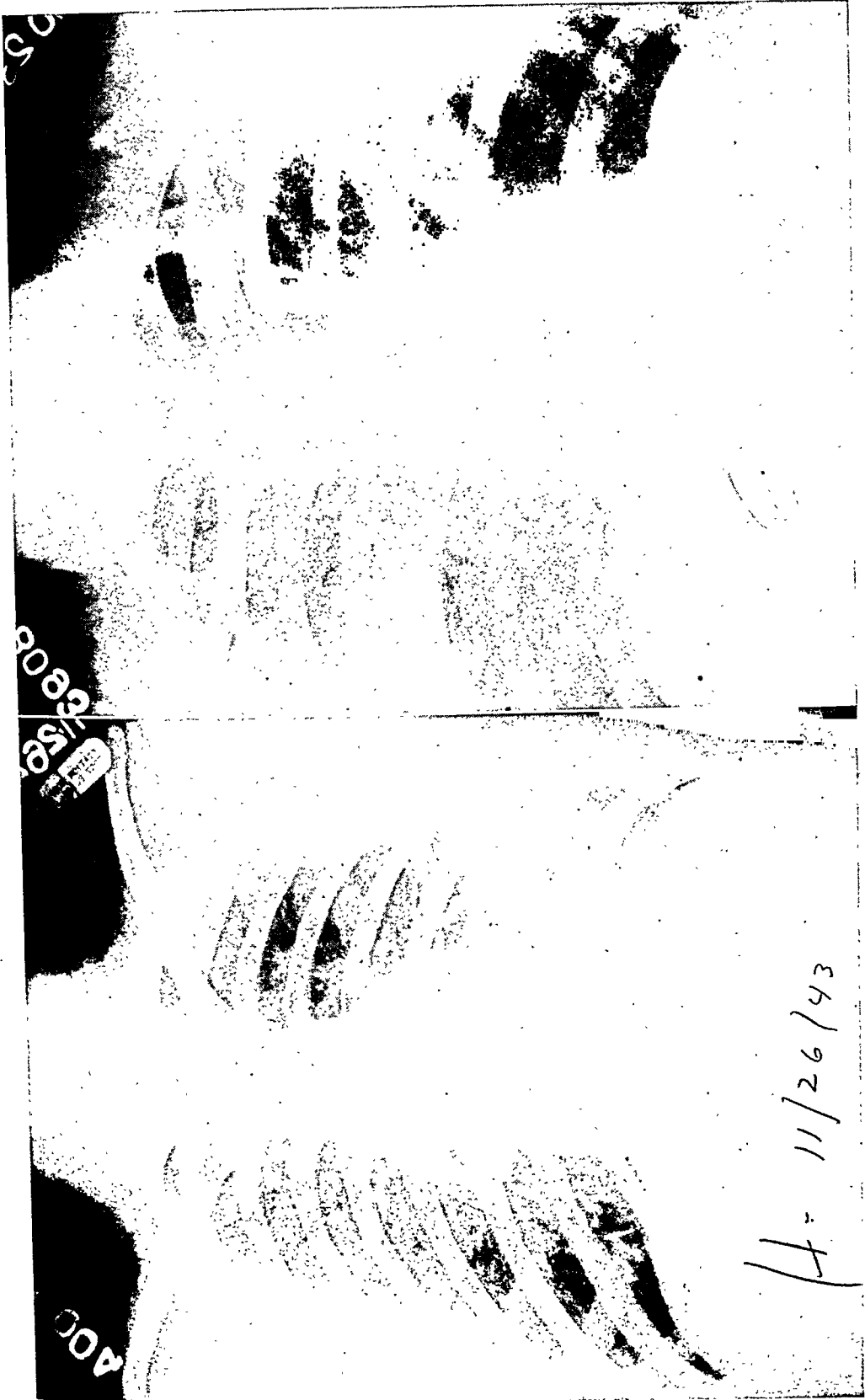


FIG. 1. Roentgenologic characteristics of the pulmonary involvement.

FIG. 2.

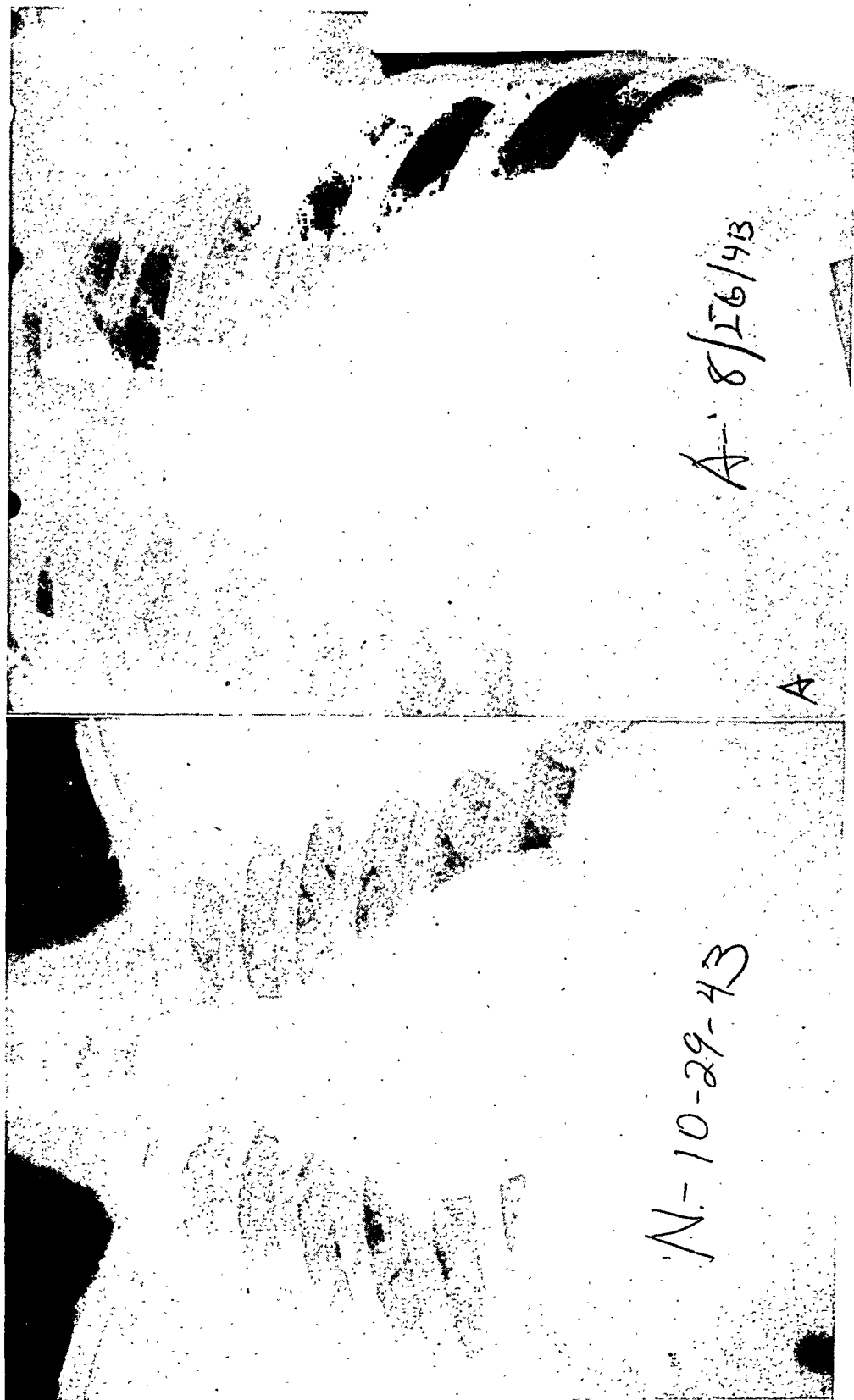


FIG. 3.

Roentgenologic characteristics of the pulmonary involvement.

FIG. 4.

observed and that present in atypical or "virus" pneumonia. Among these were the character of the cough, the asthmatic wheezing, the disparity between the physical signs and the extent of the pulmonary involvement, the roentgenologic picture and failure to respond to sulfadiazine. Recently, increased heterophile antibody titers have been reported in "virus" pneumonia.⁴⁰ We have seen three similar cases, one each in October, November and December, 1943. The first patient had an extensive involvement of the right lower lobe and his heterophile agglutination titer rose from 1:28 to

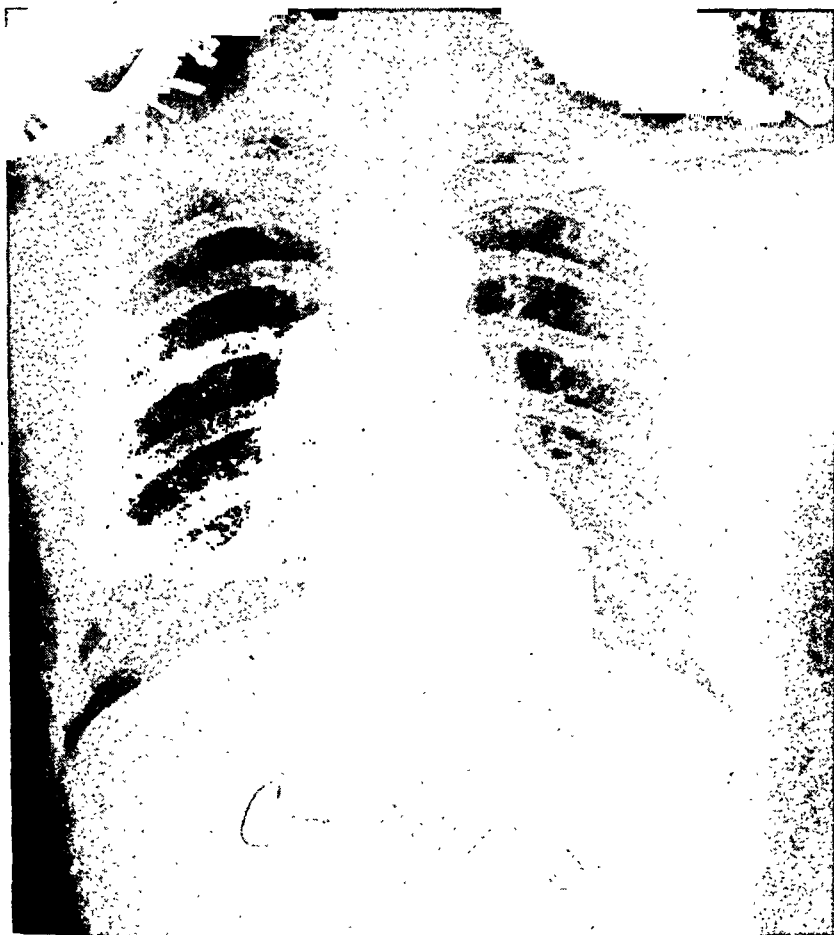


FIG. 5. Roentgenologic characteristics of the pulmonary involvement.

1:224. The second patient showed a small area of pneumonitis at the base of the left lower lobe, extending from the heart border to the periphery and his titer remained stationary at 1:112. The titer rose from 1:112 to 1:224 in the last patient, who had an involvement of the medial portions of both lower lung fields. Abnormal lymphocytes could not be found on repeated examinations, a mononucleosis never developed and the Davidsohn absorption test was negative in the two cases in which it was performed. It is evident, therefore, that differentiation between the two conditions would be in-

possible in many instances without the aid of the hematological picture. Although the pulmonary infiltrations cleared very rapidly, this phenomenon can occasionally occur in atypical pneumonia. During the course of this epidemic and especially during the winter months, sporadic cases of atypical pneumonia were admitted to the hospital. In none of these were atypical lymphocytes demonstrated.

The possibility of a secondary bacterial invasion must also be considered. Against this were the absence of significant organisms on sputum typing and culture, the clinical course, the roentgen-ray findings and the lack of the expected polymorphonuclear leukocytosis. In view of the systemic nature of the disease, there seems every reason to believe that a pneumonitis, closely resembling atypical pneumonia, can occasionally be due to the unknown etiologic agent of infectious mononucleosis.

7. *Glands.* Palpable glands were present in practically all our cases, including the insidious ones. It was, of course, impossible to state in many whether the glands were actually enlarged without knowing what they were normally like. There were, however, several aids in arriving at a decision. These were tenderness of the nodes, subsequent further enlargement or decrease in size, enlargement of glands in unusual regions and progressive involvement of different sites. When present, the glands were palpable on admission in the great majority. In a few cases, they did not appear until later in the course of the illness. Not infrequently, there was a sudden increase in the size of the glands either during the febrile period or during convalescence, in one case as late as 21 days after the onset of the illness. In others the enlargement was associated with a relapse. A progressive involvement of different sites was rarely observed, but when it did occur, it was quite striking. As hospitalization was for the most part of short duration, the glands were still palpably enlarged on discharge in the great majority. The glands usually began to shrink with the subsidence of fever, but in some patients who reentered the hospital for various reasons, they were found to be enlarged as much as six months later.

The glands were usually small, about the size of a lima bean, but were occasionally larger. The largest gland in this series was in a soldier with a German measles syndrome who had an anterior cervical node near the angle of the jaw the size of a hen's egg. They were firm, elastic and discrete. Tenderness was usually slight but not invariably so. In 11 cases, the cause of admission was the tender, swollen glands. Six of these complained solely of the cervical glands, three of both the cervical and inguinal glands, one of the cervical and axillary glands and one of the inguinal glands alone.

A considerable number complained of pain in the back of the neck and at the base of the skull. In some of these cases the tender enlarged posterior cervical and occipital glands were associated with a defensive spasm of the neck muscles and a resulting stiffness of the neck. As headache was also a prominent symptom, these cases were difficult to differentiate from meningococcus meningitis or a meningitis complicating infectious mononucleosis.

There was usually no reaction in the overlying skin. A slight edema, however, was occasionally present. When this occurred over enlarged pre-auricular and mandibular glands in two of our cases, they were mistaken for mumps.

The anterior and posterior cervical nodes were the most frequently involved. We did not notice any predilection for the left side. In order of frequency, the sites of the glandular involvement were as follows: posterior cervical, anterior cervical, axillary, inguinal, femoral, occipital, epitrochlear, submental, supraclavicular, popliteal, pre-auricular, post-auricular. Multiple regions were involved in almost all who presented glandular enlargements of any extent. Although we suspected mediastinal glandular involvement in a number of cases because of the presence of bronchitic râles or because of a spasmodic cough, we were unable to demonstrate them by roentgen-ray in any of the 53 patients so examined. Neither have we been able to palpate enlarged mesenteric glands in those with abdominal pains or with icterus.

Suppuration, attributable to infectious mononucleosis, did not occur in a single case. In one patient, who had a suppurating inguinal lymph node on admission, biopsy revealed that the disease was complicating a preëxisting lymphogranuloma inguinale.

8. *Gastrointestinal System:* The frequency of anorexia has already been mentioned in the discussion of the initial symptoms. Nausea and vomiting were uncommon and were almost wholly confined to the icteric and abdominal varieties. Constipation was the rule. There were only 27 cases who had a diarrhea either at the onset of the illness or during its course.

An interesting group was the 12 cases whose major symptom was abdominal pain. In eight of these, the pain and tenderness were confined to the right lower quadrant or shifted to this region from the epigastrium. Nausea and vomiting were frequently present. All of these cases were admitted with the diagnosis of acute appendicitis. Fortunately, the blood count on admission in all of them showed the abnormal lymphocytes and none was operated upon. In two each, the abdominal pain was generalized or confined to the right upper quadrant. In one unusual case, not included in the abdominal variety, the patient was admitted with chills, fever, headache, malaise, cough and pains in the anterior chest of two days' duration. A moderate diffuse pharyngitis, generalized glandular enlargement and a barely palpable spleen were the only findings. On the third hospital day, he complained of severe abdominal pains beneath both costal margins and a mass was palpated in the right lower quadrant. In the next two days it had increased so markedly that it was visible on inspection of the abdomen and extended to the right costal margin. Operation revealed a huge mesenteric chylous cyst which had undergone degenerative changes.

9. *Liver.* The liver was palpable in 17 per cent or half as frequently as the spleen. Usually, it was described as extending a finger's-breadth below the costal arch and not tender. In the others, the enlargement was two to

four fingers'-breadth and tenderness was present on palpation. The latter findings were almost invariably present when jaundice was manifest.

Mackey and Wakefield⁴¹ are usually credited with being the first to describe jaundice in infectious mononucleosis in 1926. Three years earlier, however, Downey and McKinlay⁴² reported transient jaundice in one of their nine patients. Since then, there have been reports of isolated cases and of the occurrence of icterus in collections of sporadic and epidemic cases. In 1944, Spring⁴³ was able to compile 35 such cases from a partial survey of the literature, exclusive of five of his own patients. We have been able to find 25 additional cases.^{42, 7, 44}

The actual frequency of this manifestation is difficult to compute for a number of reasons. In groups of reported cases, the incidence of jaundice has varied as follows: Bernstein,¹⁰ 1.5 per cent; Press, Shlevin and Rosen,^{44 (n)} 5.2 per cent; Stuart et al.,²⁸ 7 per cent; McKinlay,⁴⁵ 9 per cent; Spring,⁴³ 13 per cent; Nyfeldt,⁴⁶ 15 per cent. Collections of sporadic cases, however, have been reported in which jaundice did not appear.^{32, 33, 47} In the recent epidemic described by Halcrow and his co-workers,² jaundice did not occur, although latent jaundice was present in eight of 15 severe cases. Besides these variations in incidence, many of the reported cases cannot be accepted as unequivocal. In view of the frequent occurrence of a marked lymphocytosis and a high percentage of atypical lymphocytes in infectious hepatitis,^{8, 9} this condition cannot be excluded in most instances without a Paul-Bunnell test or a Davidsohn absorption test when the heterophile antibody agglutination titer is low or border-line. Increased sheep-cell agglutinins have not been reported in infectious hepatitis.⁹ This objection applies not only to those cases reported prior to Paul and Bunnell's publication¹² but to many of the subsequent cases. In the latter, a heterophile antibody agglutination either was not performed or was negative or it was impossible to determine from the information given, whether the seropositive cases included all patients with jaundice. We do not wish to infer that there have been no authentic cases of jaundice in infectious mononucleosis. In fact, Martin^{44 (6)} was apparently the first to describe a positive absorption test in one of his cases.

There were 34 cases (6 per cent of our series) with jaundice. The degree of icterus on admission varied considerably and depended both on the severity of the underlying process and on the length of time which had elapsed between the onset of symptoms and entrance into the hospital. Several cases were admitted at the stage in which the jaundice was subsiding.

DeVries⁴⁸ has classified the cases of infectious mononucleosis associated with jaundice into three groups: (1) Jaundice is the first symptom and is then followed by glandular enlargement. (2) Jaundice appears simultaneously with the glandular enlargement. (3) Jaundice with or without fever is the only symptom. Such a classification may be feasible in sporadic cases that are under close observation by a single observer from the onset of the disease. In this series, many cases were admitted late in the illness, while in

others, slight glandular enlargement was frequently overlooked until the blood picture called attention to the correct diagnosis.

Clinically, we were able to divide our cases into two distinct groups. In the first, consisting of 19 patients, there was no sore throat with the onset of the illness. In three of these a sore throat developed during the course of the disease; in one, as late as 20 days after admission. It is, of course, possible that a mild sore throat may have been present in some of these and forgotten by the patient. The usual history was that of anorexia, malaise, nausea and vomiting, followed in two to five days by jaundice. There was no fever or the temperature remained below 100° F. in 15. In addition, the three cases who developed a sore throat after the appearance of icterus were afebrile until this manifestation occurred. Among the symptoms that were occasionally present were pains in the right upper quadrant or epigastrium, diarrhea, chilly feelings and headache. In many of these no significant glandular enlargement was reported.

In the second group of 15 patients sore throat was always present at the onset. Fever, chills and headache were prominent complaints in addition to the symptoms described for the first group and the patients were usually hospitalized much earlier. The jaundice was also noticed two to five days after the onset. The glands were always palpably enlarged on admission.

It was our impression that the clinical picture for the entire group was indistinguishable from the ordinary case of infectious hepatitis with two minor exceptions. The icterus cleared somewhat more rapidly and the gastrointestinal symptoms were milder. The average duration of the jaundice in the 31 cases in which the onset of this manifestation could be determined with a fair degree of accuracy was only 25 days. However, the jaundice lasted for over 40 days in three, the longest period being 48 days. The shortest duration was 11 days. The well-being of the patients after the initial few days was notable. All were anxious to return to duty long before the jaundice had completely cleared. The vague digestive disturbances so frequently seen in the convalescence from catarrhal jaundice were conspicuously absent. There have been no demonstrable sequelae in those cases that we have been able to observe for as long as nine months.

As judged by the peak of the icteric index, three-fourths of the cases had jaundice of moderate severity. Excluding two cases admitted during the subsiding phase on the seventeenth and twenty-first days of their illness, the highest icteric indices recorded ranged between 24 and 100. Divided into groups, the results were as follows: 21 to 40, 6 cases; 41 to 60, 16 cases; 61 to 80, 8 cases; 81 to 100, 2 cases.

The heterophile antibody agglutination titer was 1:112 or over in 25 cases. There were three cases with titers of 1:1792. In the other nine there was either a rising titer to 1:56 or a positive absorption test.

As autopsy findings in infectious mononucleosis have been but rarely reported, an attempt was made to gather information on the nature of the liver involvement and its severity by a number of liver function tests.

The van den Bergh reaction was positive direct and indirect in all the 27 cases in which this test was performed.

The cephalin-cholesterol flocculation test as described by Hanger was done in 25 cases. The results were as follows: 0, 1 case; 1 plus, 1 case; 2 plus, 3 cases; 3 plus, 14 cases; 4 plus, 6 cases.

The total plasma cholesterol was determined in 27 cases. The highest values varied between 110 mg. per cent and 354 mg. per cent. If 250 mg. per cent is taken as the upper limit of normal, 18 were normal and nine were increased. As repeated determinations are of much more diagnostic importance than a single determination, these were performed repeatedly during the course of the illness in 12 cases. There was a correlation between the degree of icterus and the total cholesterol level in all. A rising icteric index was associated with an increase in the cholesterol and vice versa.

In the two cases in which serum phosphatase determinations were done, the values were 11.4 and 14 Bodansky units per 100 c.c., respectively.

Bromsulfalein tests were performed in 16 cases. In three the dose employed was 2 mg. per kilogram of body weight. None showed retention of the dye in 30 minutes. The dose was increased to 5 mg. per kilogram of body weight in the remaining 13 cases. In 10 of these there was a retention of the dye at the end of 60 minutes, varying between 20 per cent and 44 per cent. Only two of the 10 showed values below 30 per cent. The test was not performed until late in the course of the disease in the other three. Their icteric indices at the time of the test were 28, 21 and 11, and the retention of the dye in 60 minutes was 10 per cent, 10 per cent and 5 per cent respectively.

Glucose tolerance tests were given to 11 patients. In several of these the test was repeated at varying stages of the illness and in convalescence. The dose of glucose was 100 gm. and the criteria employed were a normal fasting blood sugar, a peak not exceeding 170 mg. per cent and a return to the initial level in two hours. Abnormal curves were found in nine, most of them markedly so. The degree of abnormality paralleled the course of the disease and returned to normal in convalescence. The two normal tests were obtained in patients in whom the jaundice was rapidly subsiding. All patients had been on a high carbohydrate, low fat diet for varying periods prior to the tests, which may have influenced their response.

In the 12 cases in which quantitative urinary urobilinogen determinations were performed, urobilinogen was present in all but not in abnormal amounts. The stools were never completely acholic, though fecal urobilinogen determinations were not done.

In summary, both the clinical picture and the liver function tests would indicate that the jaundice of infectious mononucleosis is due to a diffuse hepatitis, which is accompanied by an obstruction of the bile capillaries and a derangement of many of the functions of the liver. In the literature on jaundice in infectious mononucleosis, there are statements by several authors^{41, 44 (h), 44 (n), 48} that the icterus is secondary to an obstruction by enlarged lymph nodes, although no evidence is given for such an assumption.

There is, however, evidence that a diffuse hepatitis does occur in infectious mononucleosis.

In a case recently reported by Ziegler,^{44 (1)} in which death was due to a rupture of the spleen, the liver showed a diffuse focal hepatitis. Scattered throughout the liver were perilobular foci, composed of swollen Kupffer cells and numerous mononuclears. These were most prominent in the portal areas. There was destruction and disappearance of most of the liver cells in these foci. The small bile ducts were also involved. Many showed pericellular edema with separation of the duct epithelium from the basement membrane and others were lined with swollen epithelium which diminished or completely obliterated the lumen.

Even in the absence of jaundice the liver is frequently palpable. When the enlargement is marked and associated with a palpable spleen, the syndrome has been called the visceral form of infectious mononucleosis.^{1 (d)} It would be difficult to explain such a phenomenon on any other basis than a diffuse hepatitis. In this connection, Van Beek and Haex⁴⁹ performed a liver biopsy in a case of infectious mononucleosis without jaundice, 14 days after the onset of the illness, and found the liver cells to be interspersed with monocytes and some polymorphonuclear leukocytes. The triangles of Kiernan were rich in cells and contained numerous lymphocytes. Another puncture, performed three and one-half weeks later, revealed the liver to be practically normal except for increased lymphocytes in the triangles of Kiernan.

10. Spleen. The spleen was palpable in 35 per cent of the cases. It was usually felt about a finger's-breadth below the costal margin on deep inspiration and never exceeded three fingers'-breadth. Because of the difficulty in palpating a spleen that was only slightly enlarged, the fact that the splenic enlargement was not always present on admission but appeared later in the illness and therefore had to be persistently sought for to be discovered, and because the cases were under the care of different officers of variable experience, this percentage is far from accurate. The enlargement had rarely disappeared by the time the patient was discharged from the hospital and, in some cases, it was still palpable three months after the initial illness. Rarely, the spleen was tender on palpation.

CASE REPORTS

ACQUIRED SYPHILIS OF THE LUNG: REPORT OF A CASE WITH AUTOPSY FINDINGS AND DEMONSTRATION OF SPIROCHETES *

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ACQUIRED syphilis of the lung is an uncommon manifestation of syphilis according to many reports, particularly those written by the pathologist. Although well over 200 cases have appeared in the literature, only a minority have been confirmed by autopsy. A considerable difference of opinion concerning the diagnosis and incidence of pulmonary syphilis exists not only between the clinician and the pathologist, but also among the pathologists. This controversy can doubtless be attributed to the relatively non-specific clinical features, to the variation in diagnostic criteria employed, and lastly to the fact that such a lesion may easily be overlooked at the autopsy table because of its obscure nature and the presence of superimposed secondary infection.

Funk⁷ (1923) found only four cases of pulmonary syphilis among 1,200 patients admitted to the tuberculosis wards of the Jefferson Hospital; on the contrary, Kirkwood¹⁴ (1926) believed that about 3 per cent of all cases admitted to tuberculosis sanatoria had an associated syphilis of the lung. Claytor³ (1905) reported not a single case of pulmonary syphilis in 13,000 specimens at the Army Museum at Washington, D. C. Symmers²⁵ (1916) found 12 cases of lung syphilis in 4,800 autopsies, whereas Carrera² collected 12 cases in the study of 152 autopsied cases of syphilis. Of 6,748 autopsies performed in a recent three-year period at the Los Angeles County Hospital, I could find but two cases of acquired pulmonary syphilis, although 132 cases showed other anatomical lesions of syphilis. Howard¹¹ encountered seven cases of pulmonary syphilis in a total of 11,982 medical admissions to his clinic; four of these cases were confirmed by autopsy. Among 3,427 syphilitics at King's County Hospital, Denman⁵ reports five cases of pulmonary syphilis, four of which were proved by necropsy. In China, Lieu¹⁷ has found two cases of pulmonary syphilis in 2,800 autopsies. It is thus obvious that both clinicians and pathologists are far from being in agreement as to the true incidence of acquired pulmonary syphilis.

The following case meets the accepted criteria for the diagnosis of pulmonary syphilis, including the demonstration of the morphologically typical *Treponema pallidum*.

CASE REPORT

E. E., a 69 year old Mexican male newspaper vendor, entered the Los Angeles County Hospital on Aug. 15, 1944, complaining of generalized progressive weakness for one year, mild weight loss and frequent cough for several months. The cough

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was productive of foul, whitish-yellow mucoid sputum averaging one cup daily. For several weeks prior to admission, the patient had exertional dyspnea and an intermittent pain between the shoulder blades which was aggravated by coughing. There had been no hemoptysis, fever, or chills, and only occasional night sweats. Patient had been able to work until two days before admission. There were no tuberculous contacts, and venereal disease was denied by name and symptom. The past history was not contributory.

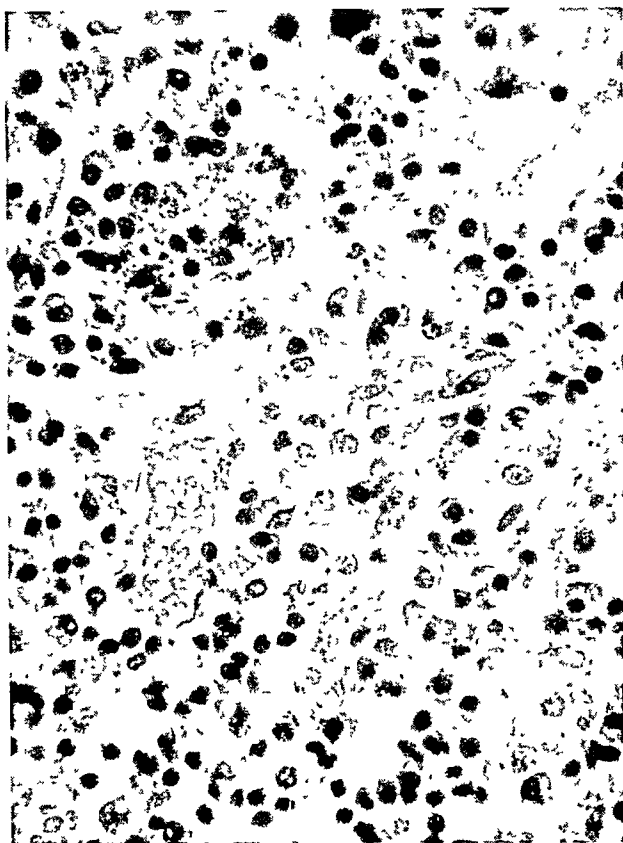


FIG. 1. Lung. Infiltration of plasma cells and lymphocytes with mild fibrosis in an active syphilitic lesion. H. & E. stain. $\times 230$.

Physical Examination. The patient was well developed, well nourished, and appeared mildly dyspneic and orthopneic. The temperature and pulse were normal. The respirations were normal in rate. The skin was clear. Examination of the eyes, ears, nose, and throat was negative. The trachea appeared in the midline. Prominence of the right side of the chest was noted, both anteriorly and posteriorly. The veins in the suprasternal notch were distended. The right lung field was dull to percussion over the lower one-half posteriorly, and increased vocal and tactile fremitus were evident together with numerous crackling râles and increased breath sounds in the same region. The left lung field was normal. The heart was enlarged, and the apex beat was palpated 2 cm. to the left of the midclavicular line. Normal sinus rhythm was present and no murmurs were heard. The blood pressure was 120 mm. Hg systolic and 60 mm. diastolic. The abdomen was negative. The fingers and toes showed a moderate degree of pulmonary osteoarthropathy. The deep reflexes were hyperactive, and there were no pathological reflexes.

Laboratory. Examination of the blood revealed a red cell count of 4,620,000 with hemoglobin of 83 per cent. The white-cell count was 11,000 with neutrophils 68 per cent, lymphocytes 32 per cent, monocytes 4 per cent, and eosinophils 2 per cent. The corrected sedimentation rate was 19, by the Wintrobe method. The blood Wassermann and Kahn reactions were four plus on two occasions. The urine was normal. The sputum was negative for tubercle bacilli on at least three examinations. The tuberculin skin test was positive with No. 3 O.T. (0.1 mg.) The coccidioidin skin test was negative (1-100 dilution).



FIG. 2. Pulmonary vessel with characteristic cellular infiltration of intima and adventitia, and widening and splitting of the internal elastic membrane. Krajian's elastic fiber stain. $\times 120$.

Course. The patient had a low grade fever, rarely above 99° F., but occasionally rising to 100° F. The initial roentgenogram of the chest taken Aug. 17, 1944, revealed a semi-confluent infiltration in the right perihilar region with marked thickening of the right hilum and diffuse involvement in the right lower lobe (figure 5). The patient continued to have a productive cough and showed little improvement. Bronchoscopy was done Sept. 8; the carina appeared markedly broadened and no evidence of intra-tracheobronchial tumor was found. A moderate amount of mucopurulent material was seen in the right main bronchus, originating chiefly from the lower lobe orifice. Lipiodol study of the right lung showed a fairly normal bronchogram in the upper and lower lobes, but very little lipiodol entered the right middle lobe. Pulmonary syphilis was considered in the differential diagnosis, and the patient was placed on potassium iodide, minims 15 three times daily. Ten days later, the roentgenogram showed no reduction in the right mid-lung density. On Oct. 28, the patient had im-

proved sufficiently to be discharged to his home, and was instructed to continue potassium iodide therapy. The patient visited the clinic on Nov. 30, and complained of a constant and severe cough which no longer responded to potassium iodide therapy. He had had a single episode of hemoptysis three weeks previously, but none since. A roentgenogram (figure 6) taken in the clinic revealed a slight decrease in density of the infiltrated area in the right mid-lung field as compared with the previous film of Oct. 19. The patient was advised to continue potassium iodide and mild sedation. On Dec. 5, the patient was readmitted to the hospital because of frequent episodes of hemoptysis, increasing dyspnea and orthopnea, and progressive loss of weight. On

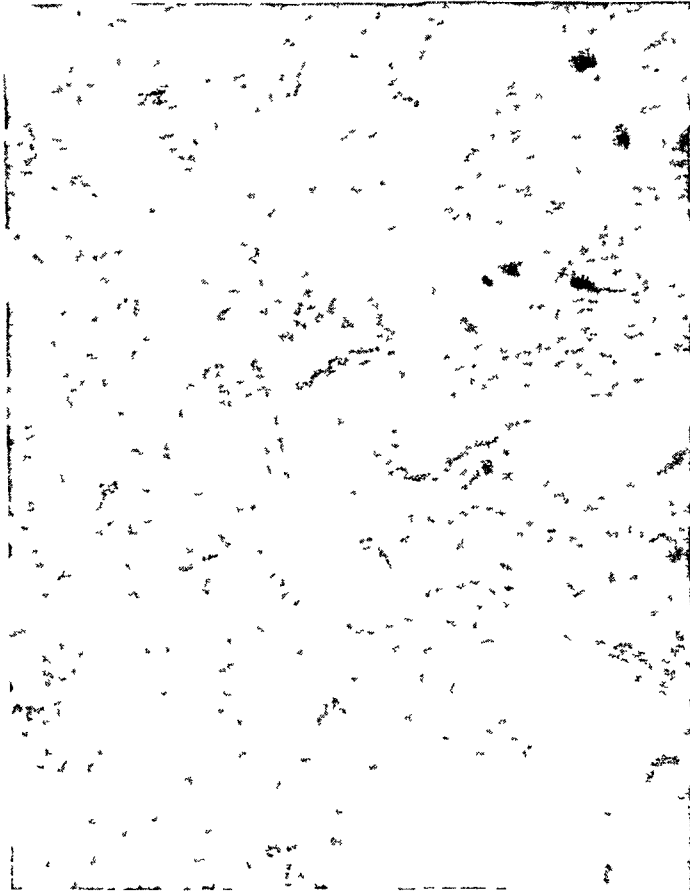


FIG 3. *Treponema pallidum* in section of lung tissue. Several others were present in this field at different levels of focus. Krajić's spirochete stain. $\times 1770$.

admission, the temperature was 102° F., and the patient was very dyspneic and orthopneic. The middle and lower portions of the right lung field were dull to percussion anteriorly, laterally, and posteriorly. Harsh breath sounds which were almost amphoric in quality were present over the right upper lobe posteriorly. Numerous crepitant râles were heard throughout both lung fields. Other physical findings were unchanged from the previous admission. The cough remained constant, with production of greenish-yellow sputum which was again negative for the tubercle bacillus. The temperature returned to normal for a few days after admission, but thereafter rose frequently to 99° and 100° F. No further roentgen study was made. On Jan. 26, 1945, the patient developed a temperature of 104° F. with signs and symptoms

of bronchopneumonia. Sulfadiazine and supportive therapy were given without response, and death occurred on Jan. 31, 1945.

Postmortem Examination. Necropsy was performed by the author five and one-half hours after death. Externally there was evidence of marked weight loss and a moderate degree of pulmonary osteoarthropathy of the extremities.

The heart was normal in all respects except for the aortic valve which showed slight widening of the commissures. The coronary ostia were of normal size. The aorta contained numerous white and yellow raised patches of tree-barking, together with longitudinal wrinkling of the intima. A moderate degree of atherosclerosis was



FIG. 4. Bronchial lymph node containing a portion of a small gumma. The central caseous zone contains nuclei in varying stages of karyorrhexis, and is bordered by an infiltration of lymphocytes and plasma cells. H. & E. stain. $\times 120$.

present, particularly in the abdominal portion of the aorta. Microscopic examination of the aorta revealed an infiltration of plasma cells and lymphocytes around the vasa vasorum of the adventitia and outer portion of the media. The media contained areas of fibrosis.

Lungs: The right lung weighed 1050 grams, and the left lung weighed 900 grams. Numerous fibrous pleural adhesions were present over both upper and middle lobes of the right lung, and fibrinous adhesions were found over the right and left lower lobes. Both lungs were subcrepitant to palpation. The perihilar region of the right lung was quite firm to palpation. A single enlarged lymph node measuring 2 by 2 cm. was found near the origin of the right middle lobe bronchus. On section this node showed an excessive amount of black pigmentation in addition to several small, grayish-white, and relatively firm areas. On section of the right lung, the perihilar regions of the

middle lobe and lower portion of the upper lobe contained several large, firm, rubbery masses. These masses were fairly well circumscribed, exhibited a fine mesh-like structure, and appeared diffusely grayish-pink in color except for scattered anthracotic deposits. The larger perihilar mass located in the middle lobe, measured 3.5 by 5 by 3.0 centimeters; it was intimately attached to the adjacent bronchi and blood vessels, and extended out along these structures toward the pleura. Dense fibrous bands radiated in all directions from this central mass (figure 7). Just beneath the pleura in the upper portion of the right lower lobe was found a small, thick-walled



FIG. 5. Initial roentgenogram. Note the dense infiltration of the right midlung field, with strand-like projections radiating toward the pleura.

bronchiectatic cavity containing a small amount of mucopurulent material. Throughout the left and right lower lobes there was gross evidence of bronchopneumonia.

Microscopic Examination of Lungs: Sections of the perihilar mass in the right lung revealed areas of fibrosis varying in density, with complete obliteration of the alveolar structure and infiltration of myriads of plasma cells and lymphocytes (figure 1). Anthracosis was marked in this area, and relatively few capillaries were present. No areas of frank necrosis were found in the parenchyma. In the bronchioles there was a mild degree of mural thickening and dilatation, with purulent exudate in the lumina. There was infiltration of the intima and adventitia of the arteries by plasma cells and small lymphocytes. The abnormally prominent internal elastic membrane was well demonstrated by special elastic tissue stains (figure 2). The elastic tissue

stain also revealed the characteristic persistence of the elastic fibers throughout the involved parenchyma. The morphologically typical spirochetes were demonstrated by the Krajan¹⁵ spirochete stain (figure 3). The spirochetes were found in moderate numbers in those areas of fibrosis showing the greatest activity. Sections of lung taken elsewhere revealed many areas of bronchopneumonia. The bronchial lymph node contained a number of small areas of gummatous necrosis with the central zone of necrosis surrounded by an exceedingly vascular fibrous connective tissue layer and many small lymphocytes and plasma cells (figure 4). Acid-fast stains of this section



FIG. 6. Later roentgenogram. Right midlung density after seven weeks of potassium iodide therapy. Minimal regression has occurred since initial film. Some lipiodol remains in the right upper lobe from previous lipiodol study.

of the lymph node were negative for the tubercle bacillus. The postmortem examination revealed no other positive findings.

Anatomical Diagnosis: Syphilis of right lung, acquired; gummata of bronchial lymph node; bronchiectasis; syphilitic aortitis; bronchopneumonia.

CLINICAL FEATURES

The clinical symptoms of pulmonary syphilis are those of any chronic pulmonary infection, and most often simulate and suggest pulmonary tuberculosis.

The symptoms in order of apparent frequency are: (1) Cough, usually of a constant and troublesome nature, with production of mucopurulent sputum in varying amount which is repeatedly negative for tubercle bacilli. (2) Dyspnea is a common symptom, often out of proportion to the physical signs, and may be due to affection of the vagus nerve. (3) Hemoptysis is relatively uncommon as compared to its incidence in tuberculosis, but may be one of the outstanding symptoms as it proved to be in the author's case. Greenfield (quoted by Howard) has said: "From evidence afforded by other cases, I am inclined to believe that a special tendency to profuse hemoptysis with slight lung disease in cases of syphilis, is dependent partly on the high vascularity of the connective tissue growth in its early stage and partly on constriction of veins by surrounding thickening." The absence of fever, profuse night sweats, and severe loss of weight is characteristic of the pulmonary lesion of syphilis, unlike that of tuberculosis. Chest pain occurs infrequently, and is produced by the involvement of the mediastinum or pleura.

The physical signs are not distinctive, and only serve to confirm the presence of a pulmonary lesion. In some cases the physical signs are minimal, but in most cases the physical examination and roentgen study reveal evidence of consolidation and infiltration of the lung fields far out of proportion to the relative well-being of the patient. This discrepancy tends to favor the diagnosis of syphilis rather than tuberculosis. The right middle and lower lobes and the left lower lobe have been designated as the most common sites of localization by many writers, although Karshner and Karshner (quoted by Howard) found upper lobe involvement to be about twice as common as lesions in the bases and right middle lobe.

The roentgenological evidence of pulmonary syphilis is at best inconclusive, although it is a necessary and valuable adjunct to the clinical diagnosis. The presence in a syphilitic patient of a persistent unilateral hilar or lower lobe density with fibrous strands extending out toward the pleura, deserves serious consideration as a manifestation of pulmonary syphilis; however, other more common disease processes produce a similar picture, namely pulmonary tuberculosis, mediastinal neoplasms, bronchiectasis, pneumoconiosis, mycotic infection, and unresolved pneumonia. Warring²⁶ declares that roentgen-ray is an "inadequate differentiator" of pulmonary syphilis and is convinced that this condition cannot be diagnosed clinically. Serial roentgenograms are essential in determining the response of the pulmonary lesion to antisyphilitic therapy.

PATHOLOGY

Almost all of the pulmonary lesions of syphilis observed at autopsy are of the late, or tertiary, stage. Secondary syphilis may involve the mucous membrane of the bronchi, as illustrated in a case with bronchoscopic examination reported by Ornstein.²⁰

Most authors agree upon the division of the lesions of acquired pulmonary syphilis into two general groups: (1) gummata, and (2) diffuse interstitial fibrosis. In his comprehensive treatise on pulmonary syphilis, Howard describes five forms as follows: (1) Gummata—the most readily recognized form, but less commonly found than formerly supposed. It is characterized by a central caseous area surrounded by a layer of vascularized fibrous tissue with an outer

layer of plasma cell and lymphocytic infiltration. (2) Chronic interstitial pneumonia, or peribronchial fibrosis, is the more common type and is similar to any chronic non-specific pneumonia. (3) Pulmonary sclerosis, or fibroid induration. This probably represents a more advanced stage of chronic interstitial pneumonia, with hard fibrous bands and nodules arranged along the bronchi, vessels, and interalveolar septa. The case herein presented best fits into this category. (4) Syphilitic phthisis is a mixed form of pneumonia, gummata, fibrosis, and cavitation.

The early stages of pulmonary syphilis have rarely been observed. Stanley (according to Carrera) has stated that in the first stages there is a diffuse mediastinitis, with intense cellular infiltration filling the alveoli, the septa, the peribronchial and perivascular tissue, with epithelial desquamation, giving a gelatinous appearance to the portion of the lung involved. Letulle, in a publication by Courcoux and Lereboullet,⁴ spoke of the "follicule elementaire" as being characteristic of the early stage of syphilis; this formation is described as a collection of spirochetes, lymphocytes, and plasma cells located in the interstitial tissue around the small bronchioles, blood vessels, and in the interalveolar septa. Letulle considers this formation to be the initial phase in the evolution of the gumma.

Many authorities have considered the gumma to be the most characteristic and important lesion of late syphilis. However, in Warthin's²⁷ opinion, the gumma is neither the most typical nor the most common syphilitic lesion in the lung or elsewhere. His concept of the pathology of syphilis is based upon the demonstration that the essential lesion of late syphilis results from the instigation of a specific and progressive inflammatory process, usually mild in degree, characterized by lymphocytic and plasma cell infiltration in the stroma. This infiltration occurs particularly about the blood vessels and lymphatics, with subsequent atrophy or degeneration of the parenchyma. The elastic fibers throughout the involved lung tissue are not destroyed, and can be demonstrated in great numbers by special elastic tissue stains. Scarring and thickening of the pleura may occur, and pleural effusion has been reported, such as the case described by Hu, Frazier, and Hsieh.¹²

In pulmonary syphilis there are characteristic changes in the pulmonary vessels. There commonly occur an endarteritis and periarteritis without appreciable damage to the media. Plasma cells and lymphocytes infiltrate the intima and adventitia; the internal elastic membrane is rarely destroyed, and usually becomes abnormally prominent with widening and splitting of this membrane. This is in contrast to the changes produced by tuberculosis, consisting of damage to all three coats of the vessel, including the destruction of the elastic fibers.

Carrera has maintained that it is only in the presence of the active, specific inflammatory process, due to the local action of the spirochete, that the positive diagnosis of syphilis of the lung can be made. If the local syphilitic process has become completely inactive, this residual fibrosis cannot be differentiated from a host of other types of pulmonary fibrosis. As long as the active lesion persists, there is reasonable assurance that the *Treponema pallidum* is present in some form. In the past only a few investigators have reported the identification of the spirochetes in lung tissue, and in many cases no attempt has been made to find them. Those reporting the presence of the spirochete include Henske (1918),¹⁰

Kielty (1916),¹³ and Warthin (1917).²⁸ McIntyre¹⁸ stated that both Koch (1907) and Vogelsang (1929) demonstrated the organism, and Howard credits Schmorl and Levaditi with this accomplishment. Windholz (1929)²⁹ searched in vain for the spirochete, but noted the presence of granular bodies within the giant cells which he thought might represent the changed or broken down form of the spirochete. It is important when looking for the *Treponema pallidum* to be mindful of the "ever-present pitfall of artefact," as Stokes²³ has aptly phrased it, and to ascertain that the organism is morphologically typical.

In view of the marked similarity of the anatomic changes in the lung produced by tuberculosis and syphilis, the differential diagnosis of these two lesions is most important. McIntyre has given an excellent summary of the important points in the differential diagnosis: (1) The caseating power of syphilis is more limited than that of tuberculosis. (2) Healed tuberculosis is circumscribed, whereas the lesions of syphilis show prolongations. (3) Giant cells are rarer in syphilis than in tuberculosis. (4) Plasma cells are rarer in tuberculosis than syphilis. (5) Anthracosis is more infrequent in the scar of syphilis than in the scar of tuberculosis. Carrera believed the opposite to be true. (6) The nodule of tuberculosis may arise without a "follicule elementaire," and may begin as an island of encapsulated bronchopneumonia. (7) The invasion of a scar with subsequent breaking down is less common in syphilis than in tuberculosis. (8) Blood vessels are more rarely attacked in syphilis. (9) The adventitia of the blood vessels is the portion that is more frequently affected in syphilis. (10) There is no epithelioid formation in syphilis as in tuberculosis. (11) The elastic tissue is better preserved in syphilitic than in tuberculous processes. (12) Syphilis produces a greater amount of connective tissue in the pleura than tuberculosis. (13) Tuberculosis does not show as many cortical pulmonary lesions adjacent to the affected pleura as does syphilis. Carrera studied the lungs of 60 cases of tuberculosis, noting the characteristic connective tissue formation and comparing it with that produced by syphilis; from this study he was convinced that it is never impossible to distinguish between these two types of fibrosis.

DIAGNOSIS

Many cases of pulmonary syphilis appearing in the literature have been diagnosed on the basis of clinical evidence alone. The relative insecurity of attempting to confirm the diagnosis of this condition clinically must be borne in mind, although one is certainly justified in making a presumptive diagnosis based upon adequate clinical evidence. Hartung and Freedman⁹ gave the following criteria for diagnosis of pulmonary syphilis: (1) History of syphilis, including evidence of stigmata of syphilis elsewhere in the body. (2) Signs and symptoms of a chronic, stubborn, and progressive pulmonary lesion. The signs are usually marked and the symptoms mild. (3) Repeated sputum examinations must be made to rule out tuberculosis, mycotic infection, and other spirochetal infections. (4) Demonstration of the *Treponema pallidum*; this is the ultimate proof. (5) Serologic examination. (6) Roentgenogram. The involvement of the root, middle lobe or bases of the lung is most suggestive. (7) The therapeutic test. (8) Anatomic confirmation whenever it is possible.

It has been stated by Allison¹ that even a presumptive diagnosis of pulmonary syphilis is not warranted until all other types of pulmonary disease have

been excluded. On the other hand, Flockmann (quoted by Denman) had previously maintained that pulmonary syphilis was the most probable diagnosis in a syphilitic patient with evidence of a chronically progressive pulmonary infiltration. This contention was upheld by Denman. As a general rule, it is wise to search thoroughly for the presence of the tubercle bacillus, for although tuberculosis and syphilis may be co-existent, it is most encouraging to know whether or not tuberculosis is confusing or complicating the picture.

The therapeutic test as a diagnostic aid has been relied upon quite heavily by some observers. Although this test admittedly offers helpful contributory evidence, I believe as many others do, that it should not receive too much emphasis; it is common knowledge that antisyphilitic therapy may cause regression and improvement in many non-syphilitic pulmonary lesions which have the same configuration on the roentgen film as does syphilis. Osler²¹ declared that the therapeutic test was by no means conclusive. Stokes advises the use of only mercury or bismuth in performing the therapeutic test, since arsphenamine and iodides have too large a margin of non-specificity. Freedman and Higley⁶ followed the clinical course of a syphilitic patient with suspected pulmonary involvement, and failed to note any response of the pulmonary lesion to antisyphilitic therapy. At autopsy a gumma, which is ordinarily amenable to therapy, was found to be the same size as shown on the initial roentgen film taken prior to treatment. In this particular case the gumma was surrounded by such a dense fibrous capsule that it was almost impossible for this lesion to have become reduced in size on serial roentgenograms. In such cases the therapeutic test would obviously be misleading.

Other antemortem diagnostic procedures have been suggested. Examination of the sputum for *Treponema pallidum* has been unsuccessful according to most authors. Munson¹⁹ has mentioned the procedure of direct lung puncture at the site of the lesion, thereby obtaining material in which the spirochete may be demonstrated. He further states that this procedure is contraindicated when one is not certain of the presence of the tubercle bacillus or other virulent organisms. Hu, Frazier, and Hsieh advised the study of aspirated pleural fluid by darkfield examination and also by inoculation of animals. They were fully aware of the scarcity of organisms in the pleural fluid, but nevertheless thought that this procedure afforded the possibility of recovering the spirochete during life.

At autopsy, the diagnosis can be confirmed with the discovery of the fairly characteristic histological changes in the lung and the identification of the spirochete. In addition to staining sections of the pulmonary lesion specifically for spirochetes, the inoculation of rabbit testes or the chimpanzee with material from the lesion has been helpful in demonstrating the presence of the *Treponema pallidum*. Unfortunately the latter procedure was not attempted in the author's case.

TREATMENT

The treatment of pulmonary syphilis is in general that of any tertiary syphilitic lesion, namely by mercury or bismuth and iodides followed by arsenicals if the clinical status of the patient permits. Penicillin should be tried in view of recent reports by Stokes et al.,²⁴ and Goldman,⁸ pertaining to the action of penicillin in late syphilis. One may question the advisability of administering antisyphilitic therapy in a suspected case of pulmonary syphilis, when a known active or

quiescent tuberculous infection is present. Both Skavlem²² and Lecaplain¹⁶ have stated that there is no reason to withhold antisyphilitic therapy in such a case for fear of adversely affecting the tuberculous process.

A successful response of gummatous lesions to specific therapy is usually obtained, and the prognosis is good unless complicated by a superimposed pneumonia, gangrene, or abscess. Howard stated that little or nothing can be expected from treatment in the sclerotic forms of pulmonary syphilis.

SUMMARY

A proved case of acquired syphilis of the lung with demonstration of the spirochete has been presented together with a review of the literature pertaining to the incidence, clinical aspects, pathology, diagnosis, and treatment of pulmonary syphilis.

Acquired pulmonary syphilis doubtless occurs far more often than commonly supposed. No doubt the reported incidence of pulmonary syphilis would rise if this diagnosis would be considered more frequently in the presence of chronic progressive pulmonary infection associated with a positive serologic reaction and other stigmata of syphilis. Moreover, the pathologist could also boost the incidence by investigating thoroughly any atypical pulmonary fibrosis or scarring encountered in cases showing collateral evidence of syphilis.

When histological changes characteristic or suggestive of syphilis are found in the lung, a thorough search for the *Treponema pallidum* should certainly be made. The demonstration of the organism by appropriate staining methods and, if possible, by animal inoculation, aids in establishing an unequivocal diagnosis.

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BIBLIOGRAPHY

1. ALLISON, R. G.: Pulmonary syphilis, Am. Jr. Roentgenol., 1929, xxii, 21.
2. CARRERA, J. L.: A pathologic study of the lungs in one hundred and fifty-two autopsy cases of syphilis, Am. Jr. Syph., 1920, iv, 1.
3. CLAYTOR, T. A.: Syphilis of the lung, Am. Jr. Med. Sci., 1905, cxxix, 563.
4. COURCOUX, A., and LEREBoullet, J.: Un cas de syphilis pulmonaire. Étude anatomoclinique, Paris med., 1934, i, 164.
5. DENMAN, H. C.: Syphilis of the lung, New York State Jr. Med., 1933, xxxiii, 1438.
6. FREEDMAN, E., and HIGLEY, C. S.: Syphilitic gumma of the lung, Am. Jr. Roentgenol., 1934, xxxi, 333.
7. FUNK, E. H.: Syphilis with pulmonary manifestations; problems of diagnosis, Med. Clin. North Am., 1923, vi, 883.
8. GOLDMAN, D.: Treatment of neurosyphilis with penicillin, Jr. Am. Med. Assoc., 1945, cxxviii, 274.
9. HARTUNG, A., and FREEDMAN, J.: Pulmonary syphilis, Jr. Am. Med. Assoc., 1932, xcvi, 1969.
10. HENSKE, J. A.: Syphilitic lobar pneumonia, Med. Fortnightly, 1908, xxxiii, 243.
11. HOWARD, C. P.: Pulmonary syphilis, Am. Jr. Syph., 1924, viii, 1.
12. HU, C. K., FRAZIER, C. N., and HSIEH, C. K.: Syphilis of the lung, Chinese Med. Jr., 1939, lvi, 431.
13. KIELTY, R. A.: Syphilis and tuberculosis in the same lung, New York State Jr. Med., 1916, civ, 252.
14. KIRKWOOD, R. C.: Syphilis of lung, Am. Rev. Tuberc., 1926, xiii, 220.

15. KRAJIAN, A. A.: The clinical application of a twenty-minute staining method for *Spirochaeta pallida* in tissue sections, *Am. Jr. Syph., Gonor. and Ven. Dis.*, 1939, xxiii, 617.
16. LECAPLAIN, J.: Syphilitic disease of lungs, *abst. Jr. Am. Med. Assoc.*, 1923, lxxxi, 256 (from *Rev. de Med.*, 1923, xl, 1).
17. LIEU, V. J.: Acquired pulmonary syphilis, *Chinese Med. Jr.*, 1940, Suppl. iii, 145.
18. MCINTYRE, M. C.: Pulmonary syphilis, *Arch. Path.*, 1931, xi, 258.
19. MUNSON, L.: Tuberculosis in paretic patients; resemblance to clinical syphilis, *Med. Bull. Vet. Admin.*, 1944, xx, 305.
20. ORNSTEIN, C. G.: Pulmonary syphilis, *Med. Clin. North Am.*, 1925, ix, 357.
21. Osler's Principles and Practice of Medicine, Christian, 13th Ed., 1938, 357.
22. SKAVLEM, J. H.: Consideration of syphilis in diagnosis and treatment of lung diseases, *Am. Jr. Syph.*, 1928, xii, 355.
23. STOKES, J. H., BEERMAN, H., and INGRAHAM, N. R., JR.: *Modern clinical pathology*, 1944, 3rd Ed., 4, 1172.
24. STOKES, J. H., STERNBERG, T. H., SCHWARTZ, W. H., MAHONEY, J. F., MOORE, J. E., and WOOD, W. B.: The action of penicillin in late syphilis, *Jr. Am. Med. Assoc.*, 1944, cxxvi, 73.
25. SYMMERS, D.: Anatomic lesions in late acquired syphilis, *Jr. Am. Med. Assoc.*, 1916, lxvi, 1457.
26. WARRING, F. C., JR.: Co-existing tuberculosis and syphilis, *Am. Rev. Tuberc.*, 1939, xl, 175.
27. WARTHIN, A. S.: The new pathology of syphilis, *Am. Jr. Syph.*, 1918, ii, 425.
28. WARTHIN, A. S.: Syphilis of the pulmonary artery: syphilitic aneurysm of left upper division, *Am. Jr. Syph.*, 1917, i, 693.
29. WINDHOLZ, F.: Ueber erworbene knotige Syphilis der Lunge, *Virchow's Arch. f. path. Anat.*, 1929, cclxxii, 76.

MYXEDEMA—CONTROLLED BY THYROID EXTRACT FOR FIFTY-TWO YEARS: REPORT OF A CASE *

By ALEX. M. BURGESS, M.D., F.A.C.P., *Providence, R. I.*

WHEN the diagnosis of myxedema has been made and thyroid therapy has produced the usual spectacular return of the patient to normal life, the question as to ultimate prognosis is asked. The usual answer is a statement that as long as the patient continues to receive thyroid in adequate dosage she will continue to live out the rest of her life unhampered by the deficiency in the activity of her own thyroid gland and that she may plan and carry on her life as may any normal person. That this is true is borne out by the facts here reported which concern a woman who developed severe myxedema at the age of 35, was put on thyroid at the age of 39 and died when almost 92 years old.

This report is of interest because it describes what is probably the longest period of successful treatment of myxedema on record. The patient herself believed that she was the first person to receive this treatment in America. She was put on thyroid by Dr. Calvin S. May of New York in 1892, one year after the first patient was given thyroid treatment in England by the late Dr. Murray. (Dr. Murray's first patient was said to have died in 1919.) As will be seen in the case report given below she was, for her age, vigorous and determined to the

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last. At times it was necessary to reduce the dosage of thyroid in order to relieve the attacks of angina pectoris which, in the last decade of her life, became very troublesome to her.

A discussion of this patient's story and her condition when she had reached the age of 84 years is given by Dr. James Howard Means.¹

CASE REPORT

Mrs. E. C. B. was first examined by the writer on February 6, 1924. She was then 71 years old, a housewife, living quietly with her husband, a retired manufacturer. When seen she was suffering from a subacute upper respiratory inflammatory process. In this attack no abnormality of her heart or lungs was made out but her blood pressure was found to be 220 mm. Hg systolic and 100 mm. diastolic.

Her family history and past history were irrelevant. She was married in 1876 and a year later gave birth to a daughter, her only child. She remained normal up to 1888 when her child died of diphtheria. This was undoubtedly a severe emotional shock to the patient. During the next few months it was noticed that her face became swollen, her hair began to fall out and her legs became "enlarged and shapeless." She was said to be anemic and it was said that for two years she ate one pound of steak a day in an attempt to correct this condition. Finally her local physicians made a diagnosis of nephritis and her husband was informed that she could not live more than six months. She was then taken to New York where she was examined by the late Dr. Calvin S. May who made the diagnosis of myxedema. According to the patient's account, authenticated by other members of her family, her condition, both physical and mental, was at this time extreme and evidently represented a very advanced stage of hypothyroidism. Dr. May placed the patient on thyroid gland but the exact form in which it was given was not remembered by the patient or the family. The patient was under the impression that she was the first person to receive thyroid treatment in America and that her case was reported by Dr. May at some medical gathering, but a search of the literature for this report has been unavailing. A letter from Dr. May's daughter to the writer states that all the doctor's papers had been examined and destroyed and no reference to the patient, who was well known to her, had been found.

After being restored to what appeared to be normal health the patient continued on thyroid and lived without acute illness except occasional "bronchial colds" until seen by the writer in 1924. She stated that at one time she took three 5 grain tablets of thyroid (Burroughs & Wellcome) a day but that the dose had been reduced to one 5 grain tablet daily and that this dose had been continued for 30 years. Following the first examination in 1924 which was made at her home she was seen casually from time to time for minor conditions. On January 29, 1926, the following examination was recorded:

Complaint: Main complaint is fatigability. Dr. Leech refers patient because of headaches and question of general condition. *Physical Examination:* Height 65 in. Temperature 95.8. Blood pressure 188 mm. Hg systolic and 92 mm. diastolic. Weight 166 lbs. Pulse 62. Patient is a well developed and nourished lady of healthy appearance for her age. Skin is clear. Mucous membranes of good color. Eyes: Pupils equal, regular and react normally; fundi normal. Hair thick and gray; not dry; in good condition; no dryness of scalp. Thyroid is not palpable and not visible. No peripheral lymph node enlargement noted. Chest symmetrical and well developed. Sides move equally with respiration. No abnormal retraction. Heart: Percussion unreliable. Rate slow: 64. Rhythm regular; no murmurs. A₂ somewhat accentuated. Lungs normal throughout. Tongue clean. Teeth: All lower molars missing and only three upper molars present. Throat clear; Tonsils small. Musculature rather flabby. Abdomen is somewhat obese, tympanitic. No spasm or tenderness.

No organs palpable. Considerable subcutaneous fat. Deep reflexes normal. Extremities negative.

Diagnosis: Myxedema (controlled by thyroid); arteriosclerosis, general; hypertensive vascular disease.

During the 20 years in which she was under observation the following information was obtained: The heart rate was always slow, usually 54 to 60 per minute, and on many occasions it was found to be very irregular. This was supposed to be due to auricular fibrillation but the electrocardiograms, of which two are reproduced, show that a marked sinus arrhythmia was present. The blood pressure was always elevated, the lowest noted being 170 mm. Hg systolic and 70 mm. diastolic, and the highest 300 mm. systolic and 160 mm. diastolic during an attack of angina pectoris on April 1, 1935. On only two or three occasions was the systolic pressure found below

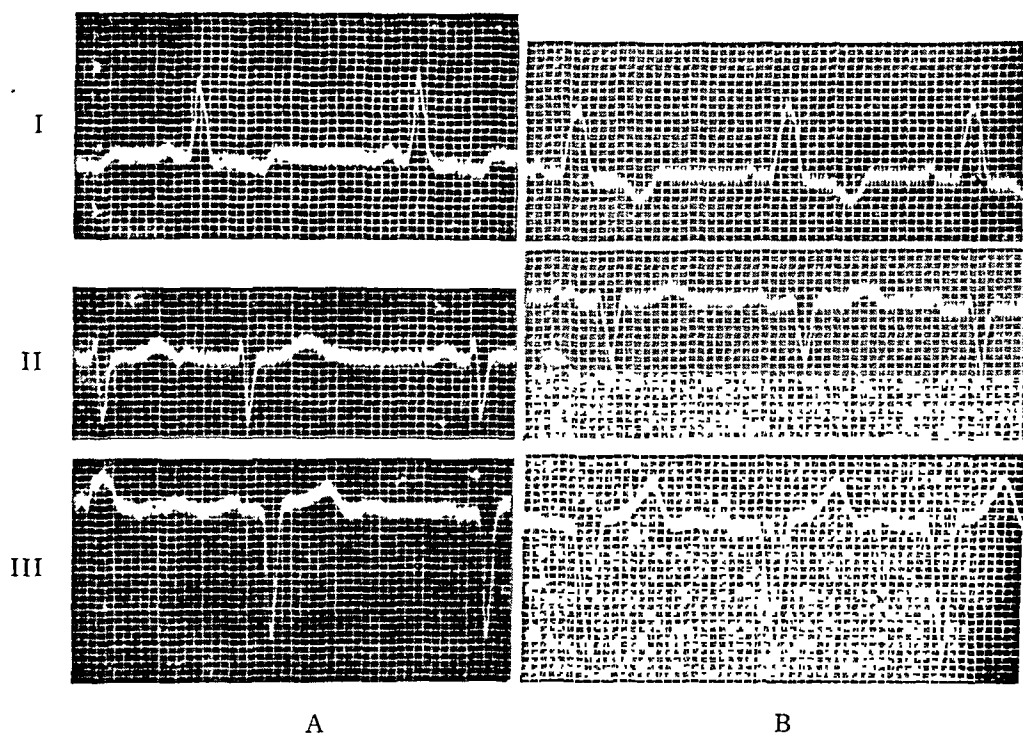


FIG. 1. A. Electrocardiogram taken in 1937; B. taken in 1940.

200 mm. Dyspnea on exertion was first noted in 1928, and basal pulmonary râles were found to be present at times in 1938. She had her first attack of severe precordial pain in February 1934, and from that time on she had periods in which such attacks were very annoying. They were usually promptly relieved by nitroglycerin. It was found in 1935 that by omitting her thyroid, or reducing its dose, the anginal attacks could be readily abolished but this was always followed by such depression and weakness that the patient invariably insisted on resuming her usual dosage. Eventually a dose was found (gr. $3\frac{1}{2}$, Burroughs & Wellcome) which was low enough to keep her fairly free from angina and high enough to prevent her from developing the symptoms of myxedema which to her were equally to be dreaded.

The diagnosis of arteriosclerotic heart disease, evidenced by the anginal attacks, was also borne out by electrocardiographic studies which showed, besides marked left axis deviation, progressive interference with intraventricular conduction (figure 1).

There was no evidence of retinal damage or of renal failure. The blood non-protein nitrogen was found to be 32.7 mg. per 100 c.c. in 1935 and the blood sugar, at this same time, 101 mg. Blood cholesterol was found to be 222 mg. in 1941, blood Wassermann and Hinton reactions were negative and the blood sugar and non-protein nitrogen values were approximately the same as they were in 1935. Several urinalyses showed traces of albumin and clumped leukocytes in the sediment, and the patient at one time suffered a mild attack of dysuria. The specific gravity of the urine specimens examined varied between 1.007 and 1.020 and at no time were casts observed.

This patient was not easily managed, being quite dictatorial and constantly given to dismissing her nurses. She could only once be persuaded to have an estimation of her basal metabolic rate which was found to be minus 15 per cent. Requests were made that she be photographed for the record but she would never allow it. She remained in control of her household up to the last few months of her life. In 1939 she was able to go away for the summer but in 1940 and 1941 a recurrence of her attacks of angina prevented her going. She had several attacks of upper respiratory infections and on at least two occasions in the last four years of her life definite bronchopneumonia developed.

During the summer of 1941 she showed rather marked peripheral edema and was treated with digitalis and mercurial diuretics with improvement. In the following winter she fell and fractured her right humerus but recovered without untoward incident.

During the fall of 1943 she became definitely weaker and spent much of her time in bed. Anginal attacks developed while she was lying in bed. Finally on the last day of December 1943 she became much weaker, there was slight fever and she was confused and disoriented. A definite diagnosis of bronchopneumonia was made and on January 8, 1943, when she was within two months of being 92 years old, she died.

POSTMORTEM EXAMINATIONS

Dr. Lester S. Round performed the necropsy and reported the following diagnoses:

Primary lesions: Bronchopneumonia and interstitial pneumonia.

Secondary or terminal lesions: None

Historical landmarks:

Atrophy and fibrosis of thyroid gland (marked).

Arteriosclerosis—generalized.

Aneurysm of abdominal aorta.

Coronary sclerosis.

Arteriosclerosis and arteriolarsclerosis of the kidneys.

Chronic fibrous pericarditis.

Chronic fibrous perisplenitis.

Chronic fibrosing pneumonitis.

Infarcts of spleen and kidney.

Chronic cystitis.

Senile genitalia.

The detailed descriptions of examination of the organs is omitted except the following:

Heart: The heart weighs 450 grams. There is some left-sided hypertrophy. The anterior and posterior descending branches of the left coronary artery show marked beading and thickening with calcification. The lumen is, in places, reduced to a very small caliber, but everywhere patent. This sclerotic condition also applies to the right coronary, but to a lesser degree. The thickness of the myocardial wall

of the two ventricles is not abnormal. The color is somewhat more brown than usual. The consistency is of normal firmness. There are no infarctions or gross evidence of scarring.

"Lungs: The right lung weighs 455 grams; the left, 285 grams. The bronchial mucosae are hemorrhagic and covered with yellowish gray purulent mucus. The right upper lobe shows a confluent bronchopneumonia. No pneumonic process is suspected in the other lobes. The blood vessels are not abnormal.

"Aorta: The aorta is very large and tortuous in the thoracic portion. In the ascending portion and in the arch there is no atheroma. The descending portion shows marked ulceration with papillary and shaggy masses of fibrin overlying ulcers from which a creamy necrotic substance can be squeezed. Over the sacral prominence is a saccular aneurysm 10 cm. long and 7 cm. wide. The wall is greatly thickened and the intima contains considerable adherent fibrin and some calcification.

"Thyroid: In the position of the thyroid is some soft whitish tissue that maintains the outline and shape of the thyroid. It appears to be entirely loose fibrous tissue and fat. Grossly no thyroid tissue is demonstrated. A brownish body, 0.5 cm. in diameter and thought to be a parathyroid gland, is attached to the left lower pole of this tissue."

Microscopic examination of the thyroid is as follows:

"Scattered through the ten sections is an occasional dilated acinus lined by a single layer of slightly flattened cuboidal cells. The lumina contain a pinkish staining homogeneous substance consistent with a colloid. Scattered through some of the sections are small islands of what appears to be parathyroid tissue."

COMMENT

The chief interest in this record arises from the fact that the patient was certainly one of the earliest patients with severe myxedema who received thyroid, that the subsequent duration of life on thyroid treatment was probably the longest yet recorded, and that she lived normally many years beyond her expectation of life in spite of the fact that during at least the last 20 years she suffered from marked hypertensive and arteriosclerotic heart disease.

BIBLIOGRAPHY

1. MEANS, JAMES HOWARD: The thyroid and its diseases, 1937, J. B. Lippincott Company, Philadelphia.

RUPTURE OF AN ANEURYSM OF A SINUS OF VALSALVA INTO THE RIGHT AURICLE*

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ANEURYSMS of the sinuses of Valsalva have been reported quite rarely; the rupture of one into the right auricle has been reported in only a few instances.

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Maude E. Abbott reported such a case in 1919.¹ One was reported by Laederich and Poumeau-Delille in 1928.² Wright³ in 1937 cited three cases in the literature other than those mentioned above and reported a fourth case. In most instances death resulted after a period of congestive heart failure.



FIG. 1. The arrow points to the opening into the aneurysm in the base of the dilated posterior sinus of Valsalva.

The rarity of the condition justifies reporting this case, an apparently healthy soldier who died within a few minutes of his first complaint, owing to the rupture of an aneurysm of a sinus of Valsalva into the right auricle.

CASE REPORT

This 22 year old soldier had had about 1½ years of military service with no physical disability. He had survived the stress of an unexpected enemy bombardment with no untoward manifestations. One day, about four months thereafter, he came off guard duty and went swimming. One-half hour later he got out of the pool and complained of precordial pain. A few minutes later, he was sitting quietly with body bent forward at the edge of the pool and was seen to roll forward into the water. The

body was removed from the water and artificial respiration was administered unsuccessfully. Death occurred within a few minutes after the first complaint.

Autopsy revealed a well developed and well nourished white male who appeared to be his stated age. Significant findings include diffuse congestion of the lungs, with a weight of 460 and 540 gm. for the right and left lungs respectively. On section, the parenchymatous tissue was congested, purplish red in color, with marked engorgement of the venous tract. Microscopically an enormous amount of congestion was evident with all vessels packed with blood cells. A considerable amount of blood pigment was



FIG. 2. Aneurysm of the sinus of Valsalva projecting into the right auricle just above the tricuspid valve with a fish-mouth rupture at the apex of the aneurysm.

present and the tissue was edematous. There was marked congestion of the liver. There was congestion of the kidneys, more marked in the medullary zone.

The cause of death was found on examination of the heart. The pericardial sac contained about 75 c.c. of clear straw-colored fluid. The epicardium presented marked engorgement of the venous and capillary network just beneath the serosa, especially marked at the apex of the heart and along the course of the main coronary vessels. The right side of the heart was markedly dilated and very flabby. On section of the myocardium, there were dark red, small, flame-like areas sharply contrasted with the rest of the muscle tissue in the upper portion of the interventricular septum near the junction of the auricular and ventricular walls. The muscle tissue appeared to be swollen. There was no evidence of rupture of any vessels. The coronary tree was

smooth throughout, but the smaller branches within the myocardium stood out more prominently than usual, especially near the involved myocardial area. Here several branches were pale and yellowish with marked pallor within the forks of these branches. The endocardium as a whole was not unusual. There was slight thickening of one of the valve leaflets of the mitral valve. The chordae tendineae were not shortened. The columnae carnae showed no evidence of scarring or thickening.

The aortic valve, at first glance, did not appear especially remarkable. The valve leaflets between the orifices of the two coronary arteries were adherent to form a single septum with a fenestrum so that there was a direct communication between these two sinuses of Valsalva. The left leaflet was much smaller than the other two leaflets. On exposing the posterior sinus of Valsalva, it was found much dilated, measuring 27 by 17 mm. with the valve opened up, and 10 mm. deep (figure 1). At the base of this sinus, there was an opening 12 mm. in diameter into an aneurysmal sac which projected into the right auricle for a distance of 2 cm. The lower margin of this sac was 3 mm. above the edge of the tricuspid valve. It was shaped like the tip of a finger cot, and had, at its apex, a fish-mouth opening extending about half way to the neck of the sac and 5 mm. across at the tip (figure 2). The aorta, above this point, was smooth and glistening, with the usual elasticity and was lined by smooth intima. The foramen ovale was completely closed.

Microscopic sections of the myocardium showed definite edema of the muscle fibers, with some foci of round cell infiltration. There was a definite paucity of red blood cells in the tissue. The aorta above the lesion was microscopically normal, and section through the aneurysmal sac showed it to be constructed of relatively acellular dense connective tissue in which no vascular elements were discerned. There were few elastic tissue fibers evident on special staining, and no evidence of inflammatory reaction.

The character of the lesion was such as to justify the opinion that it was of congenital origin.¹ The exact mechanism of death is conjecturable, but there was anatomical evidence of dilatation of the right heart and myocardial ischemia. The perforated aneurysm constituted a massive arteriovenous fistula with sudden onset. This would result in acute coronary insufficiency, and the change in the myocardium is corroborative evidence of ineffective coronary circulation. It cannot be definitely concluded that this was the cause of death for there were two other possible mechanisms. He might have developed so-called "internal tamponade" from the high pressure stream flowing from the aorta. Secondly, he might have died of cardiac shock through propulsive failure.

SUMMARY

A case of rupture of an aneurysm of the posterior sinus of Valsalva into the right auricle is reported. It resulted in sudden death in an apparently healthy soldier.

BIBLIOGRAPHY

1. ABBOTT, MAUDE E.: Clinical and developmental study of a case of ruptured aneurysms of the right anterior aortic sinus of Valsalva, in *Contributions to medicine and biological research, dedicated to Sir William Osler*, Vol. II, 1919, Paul B. Hoeber, Inc., New York.
2. LAEDERICH, L., and POUMEAU-DELILLE, G.: Anévrisme du sinus de Valsalva ouvert dans l'oreillette droite, *Bull. et mém. soc. méd. d. hôp. de Paris*, 1928, lii, 1734.
3. WRIGHT, R. B.: Aneurysm of a sinus of Valsalva with rupture into the right auricle, *Arch. Path.*, 1937, xxiii, 679.

THE INFLUENCE OF OVARIAN ACTIVITY AND ADMINISTERED ESTROGENS UPON DIABETES MELLITUS: CASE REPORT*

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MUCH time and effort have been spent in the study of the probably complex interrelationship existing between the anterior pituitary and the pancreatic islets in their regulation of carbohydrate metabolism. Many points are still obscure. However, there is evidence for an over-all antagonistic action between the hypophysis and the islets of Langerhans which is well supported by the following data.

Hypophysectomy results in a marked improvement in the diabetic state of depancreatized animals,^{1, 2} and permanent diabetes can be induced by injecting extracts from the anterior pituitary.^{3, 4, 5, 6, 7} These facts indicate that a diabetogenic principle is formed in the pituitary which in excessive amounts, or under certain conditions, proves capable of producing diabetes mellitus through a direct or indirect effect upon the pancreas. This substance probably is produced in connection with the growth hormone of the pituitary and appears to be subject to similar influences.^{4, 7, 8}

The administration of sex hormones in large doses is known to exert a suppressive action upon the gonadotropic hormone of the anterior pituitary,^{9, 10, 11, 12} as well as upon the growth,^{9, 11, 12} the lactogenic,^{13, 14, 15, 16, 17} the thyrotropic^{11, 12, 19} and the diabetogenic^{5, 8, 9, 11, 12, 18} incretions. The action of the sex hormones, particularly the estrogens, upon the diabetogenic principle of the anterior pituitary is less well understood, although some mooted points have already been clarified.

The first attempts to influence favorably the diabetic state by estrogens,^{20, 21, 23, 24} were disappointing. It should be noted, however, that the estrogenic preparations were not as potent as later forms and the dosage was comparatively small. For instance, Collens and his co-workers²³ failed to influence the diabetic state with daily doses of estrogenic substances ranging from 100 to 400 R. U. They concluded that estrogens had no effect on human diabetes. Some later workers^{22, 25, 26, 27, 28} also found estrogens had no alleviating effect or that in small doses they were actually diabetogenic. Young⁷ reported that the administration of estrogens to dogs made permanently diabetic with pituitary extract, failed to modify the diabetes.

On the other hand, evidence has slowly accumulated which shows that diabetes is favorably affected by estrogens in sufficient dosage. Barnes, Regan and Nelson⁸ were able to suppress the diabetogenic principle in depancreatized dogs with large doses of estrogens and were able to reduce and control the glycosuria. Nelson and Overholser⁵ confirmed the estrogenic suppression of the diabetogenic principle in monkeys and the relief to be obtained in diabetes by the use of ovarian follicular hormone following pancreatectomy.

The frequency of the onset or aggravation of diabetes at the menopause and

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its response to estrogenic hormone have been noted by several workers. Mazer and Israel²⁹ treated 51 menopausal cases including three with diabetes. In each of the three, diabetes was totally controlled without insulin as long as the patient received at least 2000 R. U. of estrogen every fourth day. With smaller doses the hyperglycemia and glycosuria reappeared. The authors emphasized the importance of employing massive doses, such as 10,000 R. U. every fourth day, whenever inhibition of the anterior pituitary activity was an objective.

Gessler and his co-workers³⁰ treated five diabetic women at the menopause with 10,000 R. U. of estrogen daily. In three cases, two of whom had a simultaneous onset of the menopause and diabetes, and one a diabetes appearing soon after the menopause, there was a significant lowering of the fasting blood sugar. The other two cases which were not affected by estrogens had no connection with the menopause. In four cases in which urinary assays were done, pituitary gonadotropins were present in the urine before and absent after estrogenic treatment was begun. The effectiveness of estrogens in inhibiting at least certain functions of the anterior pituitary was thus clearly shown.

Spiegelman³¹ found that the administration of 10,000 R. U. of estrogenic hormone twice a week to nine diabetic women reduced their insulin requirement. This reduction was maintained for three months after the estrogenic treatment was discontinued. Diminution of the insulin requirement was greater and more sustained in the premenopausal group than in the postmenopausal group, possibly because of the greater capacity of the pituitary to respond.

Cantilo¹⁸ used large doses of estrogen and progesterone in the treatment of menopausal and postmenopausal diabetes mellitus. Treatment was individualized in every case according to the patient's response but usually consisted of from 5 to 10 mg. of estrogen (the particular type of material not stated) and 2 to 5 mg. of progesterone three times a week. No insulin was given and an unrestricted diet was allowed. All patients showed exceptional improvement, even though several had previously exhibited glycosuria and ketonuria.

Gitlow and Kurschner³² treated 15 cases of diabetes beginning at the menopause or of preëxisting diabetes aggravated at the menopause. These workers found that improvement in the diabetes closely paralleled an improvement in the menopausal symptoms. Subjective improvement was always accompanied by a marked reduction or disappearance of the hyperglycemia and the glycosuria. The urine frequently became sugar free.

The case herewith reported is of interest if only to confirm the ability of the clinician to reduce the insulin requirement in diabetes by the administration of estrogens. Primarily, however, it engages our attention for another reason. It appears to be the first demonstration in a human being of the inhibitory action of therapeutically uninfluenced ovarian function upon the diabetogenic principle of the anterior pituitary.

CASE REPORT

S. S., a white female, was first admitted to the Metropolitan Hospital on October 28, 1943 (figure 1, twenty-first day of observation) because of an uncontrolled diabetes. She was then 31 years old, weighed 114 lbs. and was 61½ inches tall.

Her father died at the age of 83, the cause not known to her. Her mother died of carcinoma of the uterus at an unstated age. One sister aged 27 years and one

brother aged 3 years, both died of diabetes mellitus; and one brother and one sister were living and well.

In 1924, at the age of 12, the patient's diabetes was discovered and insulin started. In 1930 menstruation, although scanty, was established at 28 day intervals. In 1931 she was hospitalized for five months for the control of her diabetes. She was discharged with a measured diet and a maintenance dose of 80 units of insulin daily. From 1931 to 1940 she was admitted to a number of hospitals, usually for the control of insulin shock. On investigation of these admissions, it was found that a marked glycosuria and hyperglycemia developed shortly before the menstrual flow and ended abruptly a few days thereafter. In this post-menstrual period, hypoglycemic reactions often appeared without any premonitory symptoms. During her hospital admissions frequent insulin shocks were noted, necessitating administration of orange juice, sugar, or intravenous glucose. These shocks were first thought to be "hysterical attacks," but it was not unusual to note a marked change of fasting blood sugar in a relatively short space of time. In one instance the blood sugar dropped from 444 to 77 mg. per 100 c.c. in a space of several hours.

In 1940 the patient contracted pulmonary tuberculosis, which was arrested following the production of artificial pneumothorax. Her insulin requirement at the time her tuberculosis became quiescent ranged from 70 to 85 units daily. In 1941 she was admitted to the psychopathic ward of a hospital because of confusion following insulin shock. In 1942 she had a therapeutic abortion. The following year (March, 1943) she was readmitted because of an acute onset of lower abdominal pain, vomiting and diarrhea. At operation an endometrial cyst of the right ovary was found. The left ovary was approximately twice the normal size; it contained numerous follicular cysts and a small endometrial cyst. The right ovary and part of the left were removed. During this stay in the hospital the patient was given 75 units of insulin daily. This was distributed as follows: 35 units of protamine zinc and 15 units of unmodified insulin before breakfast, 15 units of unmodified insulin before lunch, and 10 units of unmodified insulin before supper. While in the hospital she had several mild hypoglycemic reactions. Shortly after her discharge early in June, 1943, she was readmitted for carotinemia and metro-menorrhagia. The latter was believed to be endocrine in origin. During a four months' stay in the hospital she received 70 to 80 units of insulin daily before, during, and after menstruation and 35 units daily during the "mid-period." Despite this regime she showed a marked glycosuria with ketosis at or near the time of menstruation and hypoglycemic reactions during the mid-period.

In October, 1943, she was transferred to Metropolitan Hospital. Detailed blood and urine examinations, including liver and renal function tests, revealed no pathological findings other than the diabetes. The same difficulty was experienced in controlling her diabetes as had been noted formerly. Her course is depicted graphically in figure 1. On December 4, 1943 (the fifty-eighth day of observation, figure 1), estrogenic therapy was begun in an attempt to inhibit the diabetogenic principle of the anterior pituitary. The patient received 1 mg. of estradiol dipropionate intramuscularly.* The following day, the glycosuria decreased from 4.8 per cent to 0.4 per cent. The injection was repeated on December 7, 10, 12, and 14. On December 9 the blood sugar was 70 mg. per 100 c.c., and the following morning the daily dose of insulin was reduced from 35 to 25 units. The patient was maintained on this diminished dosage of insulin throughout the following menstrual period from December 15 to 18 inclusive (days 69 to 72, figure 1). A persistently high urinary sugar with occasional acetonuria and a hyperglycemia of 400 mg. per 100 c.c. of blood developed. As in previous menstrual cycles, the blood sugar dropped within a week to 200 mg. and the urine became aglycosuric. During the mid-period from December 24

*The estradiol dipropionate (Dimenformon Dipropionate) was furnished by Dr. Leo Pirk of Roche Organon Inc., whose courtesy is herewith gratefully acknowledged.

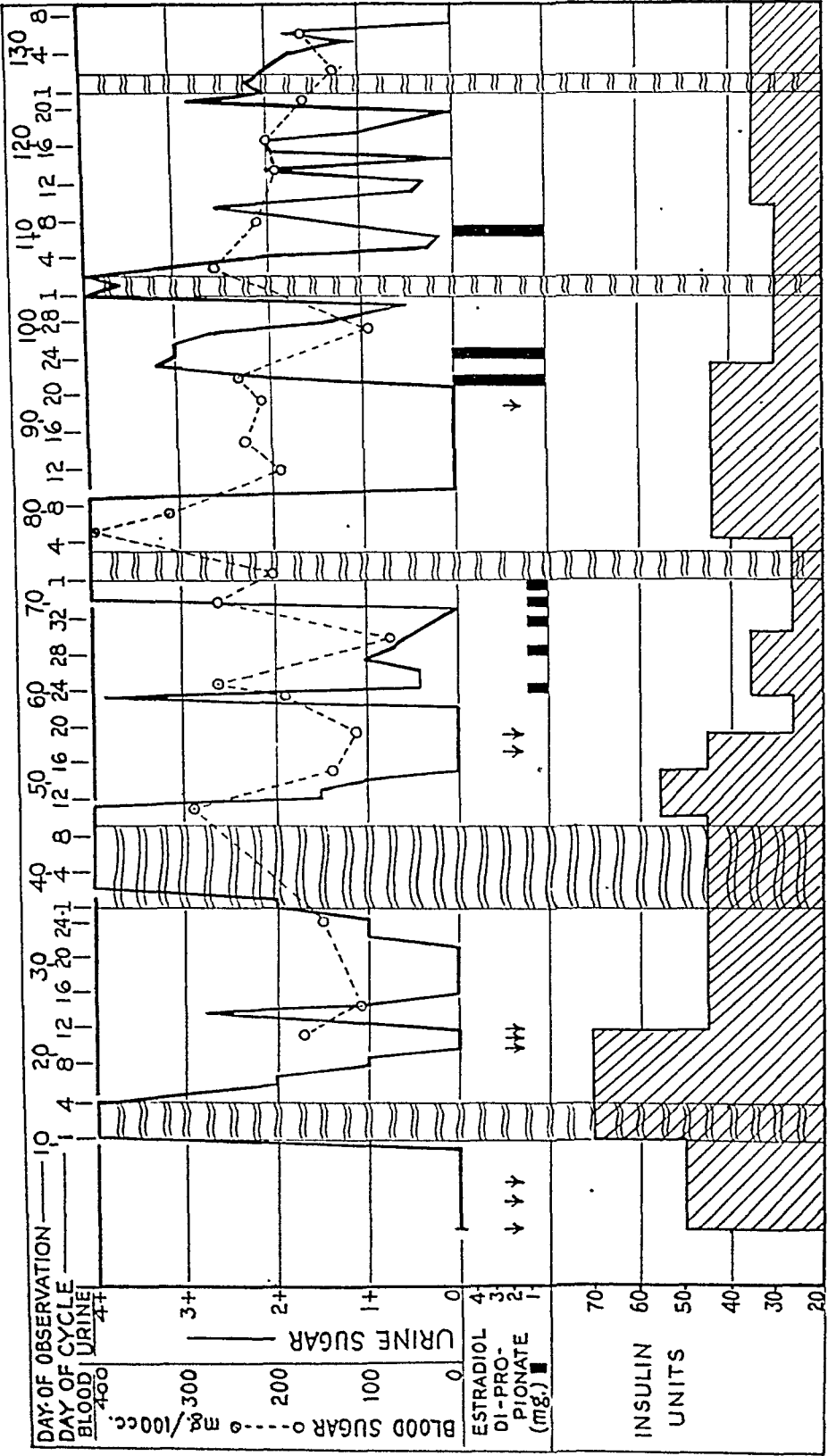


FIG. 1.
Wavy Lined Areas = Menstrual Flow Arrows = Insulin Shock
Glucose in Urine was Determined by Benedict's Qualitative Reagent; 4 Times Daily

1 + = less than 0.5%
2 + = from 0.5 to 1.0%
3 + = from 1.0 to 1.5%
4 + = 2.0% and over

until January 7 (days 78 to 92, figure 1) the fasting blood sugar varied from 200 to 230 mg. per 100 c.c. The urine was free of sugar at all times. A dose of 45 units of insulin daily, begun on December 21, was continued throughout this mid-interval. On January 5 (ninetieth day, figure 1) glycosuria of more than 3 per cent developed. The patient was given 5 mg. of estradiol dipropionate parenterally. The following day the insulin was reduced to 30 units. On January 8 (ninety-third day, figure 1) she again received 5 mg. of estradiol dipropionate; the blood sugar decreased to 95 mg. per 100 c.c. Throughout the menstrual period and for one week following it the

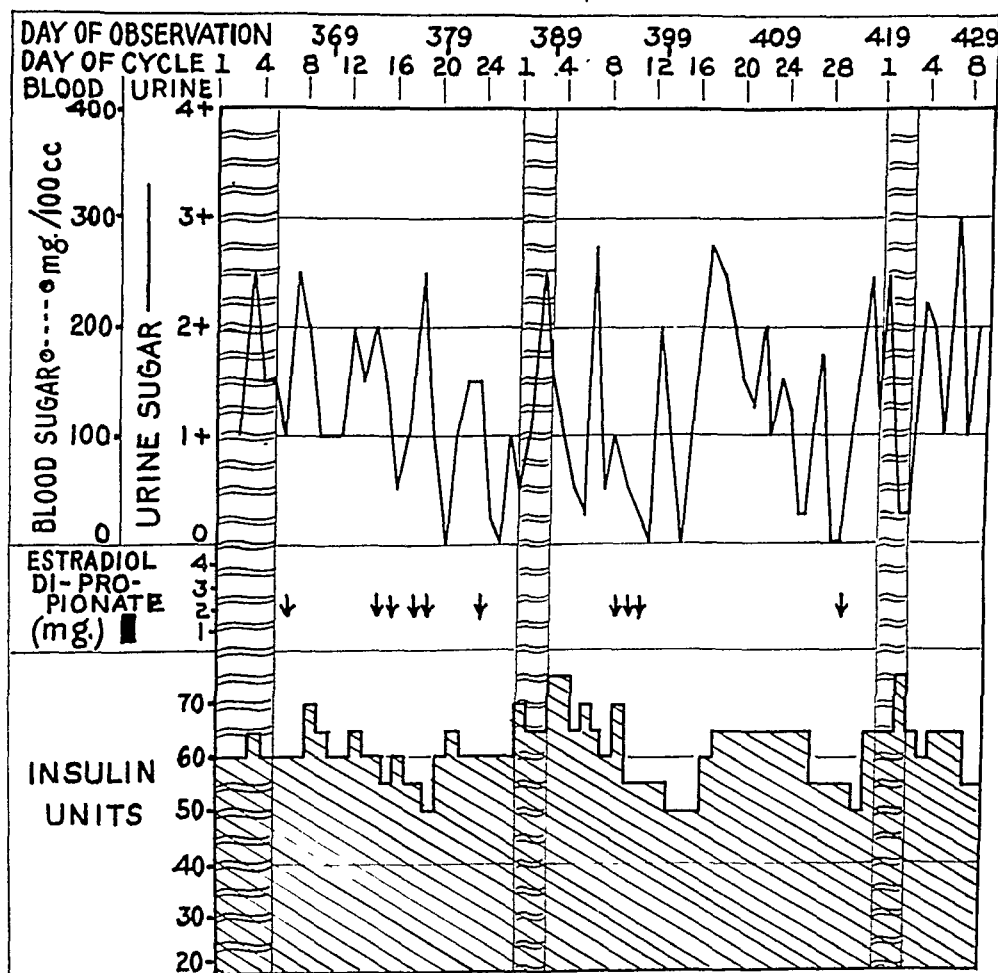


FIG. 2.

insulin dosage was maintained at 25 units daily. Although at times a glycosuria up to 3 per cent appeared, the blood sugar did not rise above 260 mg. per 100 c.c. This was a marked improvement over all previous months. Six days after the onset of her period the patient was given another injection of 5 mg. of estradiol dipropionate and the insulin was increased to and maintained at 35 units daily. Her treatment as noted was continued for the ensuing three weeks. Although there was occasionally some glycosuria, the blood sugar gradually decreased and during the following menstrual period it ranged between 125 and 155 mg. per 100 c.c. She was discharged to the out-patient department of the hospital on February 10, 1944 (one hundred twenty-

sixth day, figure 1). During the entire period of estrogenic therapy there were no "hysterical attacks." Moreover, no sedation was used. The patient stated that subjectively she felt better than she had in years.

The patient was controlled with diet and 35 units of insulin daily for almost two months following her discharge from the hospital, except for periods of 10 to 14 days about the time of menstruation. At such times it was necessary to increase the insulin to 40 units daily.

Following the complete cessation of estrogenic therapy she gradually reverted to her former status (figure 2). In other words, during the mid-period her insulin requirement ranged from 45 to 60 units and during menstruation 10 to 20 additional units were required. When estrogenic therapy was again resumed, the insulin requirement decreased although not as dramatically as before. For the past year the patient has been ambulatory and while mild insulin reactions have occurred, no hospitalization has been necessary.

DISCUSSION

Experimental and clinical evidence points to the fact that large doses of estrogenic hormone have an inhibitory effect on the diabetogenic principle of the anterior pituitary. Conversely, small doses of estrogens either have no effect or are actually diabetogenic. Estrogenic hormone in adequate doses is of greatest value in diabetes when the disease has been initiated or aggravated by an increased liberation of pituitary hormone due to diminished ovarian function. This is particularly true if therapy is instituted before the changes caused by such hormonal imbalance have become irreversible.

How great a part the diabetogenic principle of the pituitary plays in the etiology of human diabetes has not been definitely established, but accumulating evidence accords it an increasingly important rôle. Animal experiments have shown that the diabetes induced by pituitary injections can be made permanent by continuing the injections for a sufficiently long period of time.^{3, 7} Does human diabetes become permanent in a similar way? Is that why rapid improvement and easily controlled diabetes usually follow prompt treatment? Lukens and Dohan³³ found that 17 of the 19 patients who had remissions were first seen within four months of the clinical onset of their diabetes. Was this so early that the abnormal changes in the pancreas were still reversible?

The present case is unique in that fluctuations in the patient's own blood and tissue stores of hormone were sufficient to alter her carbohydrate tolerance with every successive menstrual cycle. The temporal relationships of these hormonal changes accord well with the early findings and conclusions of Frank and Goldberger³⁴ regarding estrogens in circulating and menstrual blood. These workers found an abrupt increase in the amount of female sex hormone in the blood at the mid-interval period, that is between the tenth and fifteenth days. An abrupt decrease was always noted at the onset of flow. Other investigators have made similar observations.^{35, 36, 37, 38, 40, 41, 42} It will be noted that our patient has uniformly lost tolerance with the onset of menstrual flow and regained it at mid-interval. The most unusual feature of her entire problem is the degree to which these changes go. They are sufficient to produce coma with menstruation. However, if her diet and insulin are adjusted to prevent such a complication and are not changed again in the middle of the cycle, then hypoglycemic shock invariably occurs.

The important rôle of the variations in estrogenic hormone in the above

alterations is further substantiated by the fact that relatively large doses of estradiol dipropionate have not only improved her glucose tolerance, but have also prevented violent fluctuations in the diabetic status which in the past has led to alternate periods of coma and shock. In other words, during the mid-period of the menstrual cycle when estrogen in the circulating blood is at its peak, the insulin requirement in this patient is much less than near and during the menses when the estrogen level is low. Therefore, her insulin requirement was dramatically decreased by the administration of estrogen. Moreover, the administration of large doses of estrogens has tended to stabilize the diabetic state as shown by the cessation of the previously frequent episodes of hypoglycemia and ketosis.

BIBLIOGRAPHY

1. HOUSSAY, B. A., and BIASOTTI, A.: The hypophysis, carbohydrate metabolism and diabetes, *Endocrinology*, 1931, xv, 511.
2. REGAN, J. F., and BARNES, B. O.: The relation of the hypophysis to experimental diabetes, *Science*, 1933, lxxvii, 214.
3. YOUNG, F. G.: Permanent experimental diabetes produced by pituitary (anterior lobe) injections, *Lancet*, 1937, ii, 372.
4. EVANS, H. M., MEYER, K., SIMPSON, M. E., and REICHERT, F. L.: Disturbance of carbohydrate metabolism in normal dogs injected with the hypophyseal growth hormone, *Proc. Soc. Exper. Biol. and Med.*, 1931-32, xxix, 857.
5. NELSON, W. O., and OVERHOLSER, M. D.: Effect of oestrin injections upon experimental pancreatic diabetes in the monkey, *Proc. Soc. Exper. Biol. and Med.*, 1934-35, xxxii, 150.
6. HOUSSAY, B. A.: Diabetes as a disturbance of endocrine regulation, *Am. Jr. Med. Sci.*, 1937, cxcii, 581.
7. YOUNG, F. G.: The anterior pituitary gland and diabetes mellitus, *New Eng. Jr. Med.*, 1939, ccxxi, 635.
8. BARNES, B. O., REGAN, J. F., and NELSON, W. O.: Improvement in experimental diabetes following administration of amniotin, *Jr. Am. Med. Assoc.*, 1933, ci, 926.
9. SPENCER, J., D'ARMOUR, F. E., and GUSTAVSON, R. G.: Further studies on estrin—hypophyseal antagonism in the white rat, *Endocrinology*, 1932, xvi, 647.
10. MEYER, R. K., LEONARD, S. L., HISAW, F. L., and MARTIN, S. J.: The influence of estrin on the gonad-stimulating complex of the anterior pituitary of castrated male and female rats, *Endocrinology*, 1932, xvi, 655.
11. ZONDEK, B.: The inhibitory effect of follicular hormone on the anterior lobe of the pituitary gland, *Lancet*, 1936, i, 10.
12. ZONDEK, B.: Impairment of anterior pituitary functions by follicular hormone, *Lancet*, 1936, ii, 842.
13. MAZER, D., ISRAEL, S. L., and RAVETZ, E.: The synthetic estrogen stilbestrol, *Jr. Am. Med. Assoc.*, 1941, cxvi, 675.
14. HEPP, J. K.: Stilbestrol: A clinical and investigational study, *Pennsylvania Med. Jr.*, 1941, xlv, 718.
15. WINTERTON, W. R., and MACGREGOR, T. N.: Clinical observations with stilbestrol, *Brit. Med. Jr.*, 1939, i, 30.
16. CONNALLY, H. F., JR., DANN, D. I., REESE, J. M., and DOUGLASS, L. H.: A clinical study of the effects of diethylstilbestrol on puerperal women, *Am. Jr. Obst. and Gynec.*, 1940, xl, 445.
17. MUCKLE, C. W.: The suppression of lactation by stilbestrol, *Am. Jr. Obst. and Gynec.*, 1940, xl, 133.
18. CANTILO, E.: Successful responses in diabetes mellitus of the menopause produced by the antagonistic action of sex hormones on pituitary activity, *Endocrinology*, 1941, xxviii, 20.

19. GOLDMAN, S. F., GOLDMAN, A., and KURZROCK, R.: The treatment of menopausal hyperthyroidism with estrogenic substance, *N. Y. State Jr. Med.*, 1940, xl, 1178.
20. KAUFMANN, E.: Ovarialhormon, Insulin und Kohlenhydratstoffwechsel, *Deutsche med. Wchnschr.*, 1929, lv, 650.
21. GULICK, M., SAMUELS, L. T., and DUEUL, H. J., JR.: The sexual variation in carbohydrate metabolism, *Jr. Biol. Chem.*, 1934, cv, 29.
22. YOUNG, F. G.: Influence of estrogens on experimental canine diabetes mellitus, *Lancet*, 1941, i, 600.
23. COLLENS, W. S., SLOBODKIN, S. G., ROSENBLIETT, S., and BOAS, L. C.: The effect of estrogenic substance on human diabetes, *Jr. Am. Med. Assoc.*, 1936, cvi, 678.
24. ZUNZ, E., and LABARRE, J.: Contributions a l'etude des effets des hormones sexuelles sur la regulation de la glycemie, *Arch. Internat. de Physiol.*, 1939, xlviii, 287.
25. INGLE, D. I.: Diabetogenic effect of stilbestrol in force-fed normal and partially depancreatized rats, *Endocrinology*, 1941, xxix, 838.
26. DOLIN, G., JOSEPH, S., and GAUNT, R.: Effect of steroid and pituitary hormones on experimental diabetes mellitus of ferrets, *Endocrinology*, 1941, xxviii, 840.
27. GRIFFITHS, M., MARKS, H. P., and YOUNG, F. C.: Influence of estrogens and androgens on glycogen storage in fasting rat, *Nature*, London, 1941, i, 601.
28. LAWRENCE, R. D., and MADDERS, K.: Human diabetes treated with estrogens, *Lancet*, 1941, i, 601.
29. MAZER, C., and ISRAEL, S. L.: Studies on the optimal dosage of estrogens, *Jr. Am. Med. Assoc.*, 1937, cviii, 163.
30. GESSLER, C. J., HALSTED, J. A., and STETSON, R. P.: The effect of estrogenic substance on the blood sugar of female diabetics after the menopause, *Jr. Clin. Invest.*, 1939, xviii, 715.
31. SPIEGELMAN, A. R.: Influence of estrogen on the insulin requirement of a diabetic, *Am. Jr. Med. Sci.*, 1940, cc, 228.
32. GITLOW, S., and KURSCHNER, D. M.: Estrogen, diabetes, and the menopause, *Arch. Int. Med.*, 1943, lxxii, 250.
33. LUKENS, F. D. W., and DOHAN, F. C.: Remissions of diabetes mellitus, *Pennsylvania Med. Jr.*, 1944, xlvii, 1.
34. FRANK, R. T., and GOLDBERGER, M. A.: The female sex hormone, its occurrence in the circulating and menstrual blood of the human female, *Jr. Am. Med. Assoc.*, 1926, lxxxvi, 1686.
35. FLUHMAN, C. F.: A new procedure for the demonstration of estrin in the blood of women, *Endocrinology*, 1934, xviii, 705.
36. PALMER, A.: Hormones in urine of a normal non-pregnant woman, *Proc. Soc. Exper. Biol. and Med.*, 1937-38, xxxvii, 273.
37. YERBY, L. D.: Relation of urinary excretion of estrone to menstrual cycle of normal women, *Proc. Soc. Exper. Biol. and Med.*, 1937, xxxvi, 496.
38. GUSTAVSON, R. G., and GREEN, D. R.: The quantitative determination of the amount of estrogenic substances excreted daily in the urine of the normal female, *Jr. Biol. Chem.*, 1934, cv, 24.
39. SMITH, G. V., and SMITH, O. W.: Quantitative determination of urinary oestrin, *Am. Jr. Physiol.*, 1935, cxii, 340.
40. D'AMOUR, F. E.: The estrin-gonadotropin relationship during the menstrual cycle, *Am. Jr. Physiol.*, 1940, cxxix, 342.
41. GUSTAVSON, R. G., MASON, L. W., HAYS, E. E., WOOD, T. R., and D'ARMOUR, F. E.: The quantitative determination of estrogenic substances in normal female urine during the menstrual cycle, *Am. Jr. Obst. and Gynec.*, 1938, xxxv, 115.
42. WERNER, S. C.: A quantitative study of the urinary excretion of hypophyseal gonadotropin, estrogen, and androgen of normal women, *Jr. Clin. Invest.*, 1941, xx, 21.

EDITORIAL

MURINE TYPHUS FEVER

THIS disease, which clinically resembles a mild form of "classical" typhus fever, seems to have been first recognized as typhus fever by Paullin¹ in Atlanta, Georgia, in 1913. Following his report, similar cases were observed in several other cities along the South Atlantic and Gulf Coasts of the United States. It was not until 1926, however, that Maxcy² pointed out clinical and epidemiological differences between these cases and typhus fever as observed in the northeastern United States and in Europe. In 1931 Dyer et al.³ brought proof that the infectious agent, a Rickettsia, exists naturally in the rat, and that it is conveyed from rat to rat by the rat flea and the rat louse. It is conveyed to man by the rat flea, not by the bite but by rubbing or scratching the infected feces of the flea into the skin.

The clinical features of the disease have been described repeatedly and recently have been reviewed by Stuart and Pullen⁴ (in New Orleans) and by Miller and Beeson⁵ (in Atlanta). Although the disease is reasonably familiar to physicians where it has been prevalent in the southeastern Seaboard, as it is increasing in frequency and extending northward into areas where it is not well known, a brief description seems appropriate.

The disease, as a rule, occurs sporadically in the endemic areas and is met with chiefly in foodhandlers and others whose occupation brings them into contact with rats. There is probably little difference in susceptibility as regards age, race or sex, except as these factors affect exposure to infection or ease of recognition. The incubation period is usually between eight and 12 days with extremes of five to 15 days.

Although for a few days there may be mild premonitory symptoms such as general aching, slight fever, anorexia and malaise, the onset is characteristically abrupt. There is severe and protracted headache, fever, general malaise, and aching in the muscles. Chills are frequent during the first few days, and gastrointestinal disturbances are common—anorexia, nausea, vomiting, constipation or more rarely diarrhea. Coryza and cough, usually unproductive, occur in about half the cases.

The temperature rises rapidly to a maximum of 103° to 105° F., being sustained during the first week or 10 days, but showing a tendency to partial morning remissions during the second week. The fever usually terminates by a rapid lysis, more rarely by crisis, after two to three weeks.

¹ PAULLIN, J. E.: Typhus fever with a report of cases, *South. Med. Jr.*, 1913, vi, 36.

² MAXCY, K. F.: An epidemiological study of endemic typhus (Brill's disease) in southeastern United States, *Pub. Health Rep.*, 1926, xli, 2967.

³ DYER, R. E., et al.: Experimental transmission of endemic typhus fever of the United States by the rat flea, *Pub. Health Rep.*, 1931, xli, 2415.

⁴ STUART, B. M., and PULLEN, R. L.: Endemic (murine) typhus fever: Clinical observations of 180 cases, *Ann. Int. Med.*, 1945, xxiii, 520.

⁵ MILLER, E. S., and BEESON, P. B.: Murine typhus fever, *Medicine*, 1946, xxv, 1.

The first and the only highly distinctive feature of the disease is the rash, which occurs in 80 to 90 per cent of white patients, but is often inapparent or overlooked in negroes. It appears usually on the fifth to the eighth day, rarely earlier. It appears first and in greatest profusion on the chest and upper abdomen. It may be sparse and limited to a few spots in this region. Later it spreads, as a rule, involving also the back and proximal segments of the limbs. The palms, soles and face are rarely involved. The rash is composed of small, bright-red macules or slightly elevated papules 2 to 5 mm. in diameter, which fade on pressure. Later they become more dusky, do not fade entirely on pressure, and in severe cases may become petechial. They usually fade after about six days, leaving a brownish discoloration. The eruption may at times be confused with that of typhoid fever, measles, meningococcemia, drug rashes, and particularly tick-borne Rocky Mountain spotted fever. Typically the distribution is different in the latter, starting on the wrists and ankles, then extending to the trunk, and often involving the palms and soles and occasionally the face. It is much more often hemorrhagic. Differentiation of mild cases of Rocky Mountain spotted fever may be quite difficult and require animal inoculation or crossed immunity tests.

Severe manifestations and serious complications are uncommon. Occasionally there may be lethargy or stupor, or confusion and delirium. Bronchopneumonia has been reported in about 5 per cent of the cases. Serious cardiac complications are rare. The mortality is less than 5 per cent.

Physical examination reveals little that is distinctive besides the rash. The spleen is palpable in about 30 per cent of the cases. The leukocyte count is usually about normal, with a tendency to leukopenia during the first week and to a slight leukocytosis during the later period.

After about eight days (five to 20 days) the Weil-Felix reaction (agglutination of the OX₁₉ strain of the proteus bacillus) usually becomes positive. A titer less than 1-80 is of no significance, and titers of 1-320 and 1-640 have been observed in conditions other than Rickettsial infections. It often reaches 1-2000 or higher. A similar reaction is given by patients with classical typhus and with Rocky Mountain spotted fever.

A positive diagnosis can usually be reached by intraperitoneal injection into nearly grown male guinea pigs or white rats, of 1 c.c. of blood obtained during the early stage of the disease. After an incubation period of five to nine days the animal shows a fever (104.5° to 104.5° F.) lasting several days and commonly accompanied by erythema and edema of the scrotal skin. Many Rickettsiae can be demonstrated in the cells scraped from the tunica vaginalis. Such scrotal lesions are not produced by other species of Rickettsia, although thromboses and necroses of the scrotal skin may occur after injection of blood from cases of the severe form of Rocky Mountain spotted fever.

A diagnosis can also be made by biopsy of a macule in the skin. The characteristic lesion is swelling and proliferation of the endothelium of the

small vessels. In suitably prepared sections the organisms can be recognized (by experienced observers) in the cytoplasm of the endothelial cells. In Rocky Mountain spotted fever the organisms characteristically invade the nucleus, and the smooth muscle cells of the arterioles are involved.

The disease is caused by *Rickettsia mooseri*, which is closely related to *R. prowazeki*, the cause of classical (European, epidemic, louse-borne) typhus fever. Like the other Rickettsiae, it is a minute coccoid to rod-shaped organism which is not demonstrable by the usual aniline dyes but stains readily by special methods (Castaneda or Giemsa stains). They are not filtrable (except the species *R. burneti*, which causes Q fever), but resemble viruses in growing only within living cells. They can be grown in suitable tissue cultures and in the yolk sac of developing chick embryos. Guinea pigs which have been inoculated with either *R. mooseri* or *R. prowazeki* usually recover and are immune to reinoculation. There is a cross immunity between the two species. The two diseases are differentiated mainly by the difference in epidemiology and the milder clinical course of the endemic type (mortality less than 5 per cent as contrasted with 20 to 80 per cent in epidemic louse-borne typhus). The Rickettsiae can be differentiated by complement fixation tests (Plotz), however, and most readily by animal inoculation. *R. prowazeki* does not cause the scrotal reaction characteristic of *R. mooseri*.

Although many epidemics of louse-borne typhus fever have occurred in the United States following introduction of the infection from abroad, none has been traced to any endemic focus in this country. Sporadic cases of typhus fever, however, have been recognized in the northeastern United States since Brill's description of this form of the disease (1898-1911). As there was little evidence of contagiousness and as the disease was mild and clinically resembled the typhus fever observed in the Southern States, it was assumed that they were identical. Later, however, Zinsser⁶ showed that the agent obtained from Brill's disease was identical with that of European (louse-borne) typhus in its pathogenicity and immune reactions. It, therefore, seems unwarranted to apply the term Brill's disease to murine typhus. There is no obvious reason why epidemics might not arise from such cases under suitable conditions, though thus far this has not occurred.

Although murine typhus has been commonly termed endemic, flea-borne typhus, recent observations have shown that it can be conveyed from man to man by the body louse (by the inoculation of the feces or crushed tissue of the louse, not by the bite). When conditions were suitable, with overcrowding and heavy louse infestation, epidemics of murine typhus have occurred (in Mexico).⁷

It is also possible that infection may be acquired without actual contact with fleas. Rickettsiae remain viable in desiccated feces of the flea, and there

⁶ ZINSSER, H., and CASTANEDA, M. R.: On the isolation from a case of Brill's disease of a typhus strain resembling the European type, *New England Jr. Med.*, 1933, ccix, 815.

⁷ ZINSSER, H.: *Virus and rickettsial diseases*, 1941, Harvard University Press, Cambridge, p. 872.

is some reason to believe that infection may be acquired by inhalation. Rats can also be infected by feeding infectious material. As *Rickettsiae* have been demonstrated in rat urine, it seems likely that food contaminated by infected rat urine may be a potential source of infection in man.

Brigham and Pickens⁸ have reported finding murine typhus in house mice. The practical significance of this is not yet known, but if the infection in mice behaves as it does in rats and becomes wide spread, the possibilities of its transmission to man are obvious.

Although the practical significance of these latter observations is not yet known, it is possible that infection by inhalation or ingestion may have contributed to the recent geographical spread of the disease. Originally limited largely to the coastal cities, it has gradually spread northward, reaching West Virginia, Tennessee, Arkansas and Iowa, and has been found in Cincinnati, Cleveland and Washington, D. C.⁹ It promises to become wide spread in this country wherever rats abound. It is widely distributed, particularly in coastal regions, throughout the world.

There is no specific treatment. *Rickettsiae* are not susceptible to sulfonamides, penicillin or other known forms of chemotherapy. Immune sera have not yielded any convincing benefit. Practically preventive measures are limited largely to reduction of the rat population, particularly rat-proofing of buildings containing food stuffs and continuous efforts at trapping and poisoning. Considerable protection, probably relatively brief, is afforded by suitable vaccine. Practically, however, its use would be limited to those whose occupation exposes them to unusual risk of infection, or to communities if an actual epidemic should arise. Fortunately the mortality has been very low except in those debilitated by malnutrition or chronic disease.

⁸ BRIGHAM, G. D., and PICKENS, E. G.: Strain of endemic typhus fever virus from house mice (*Mus musculus musculus*), Pub. Health Rep., 1943, lviii, 135.

⁹ TOPPING, N. H., and DYER, R. E.: Recent extension of typhus in the United States, Am. Jr. Trop. Med., 1943, xxiii, 37.

REVIEWS

The Diagnosis of Nervous Diseases. By Sir JAMES PURVES-STEWART, K.C.M.G., C.B. 880 pages; 22 × 14.5 cm. 1945. Williams & Wilkins Company, Baltimore. Price, \$11.00.

This is the latest edition of a standard clinical guide to neurologic and psychiatric conditions. In spite of war time paper shortages, it is well printed on excellent quality paper. It is not a complete textbook in any sense and deals little with the treatment of the conditions it describes. It is well illustrated with many clear and original diagrams of nerve tracts, as well as numerous photographs of clinical conditions. The style is marked by the clarity of writing for which British authors are justly famed.

Revising it in the midst of World War II, the author was able to introduce the description and discussion of many new neurologic syndromes, such as the crush syndrome and the transient blindness of aviators. Included also is much recent material concerning endocrine physiology.

The book is weak in its discussion of psychological and psychiatric conditions. The author gives in detail the technic of giving the Stanford Revision of the Binet Simon intelligence test. Unfortunately the 1916 revision is used and not the 1937 revision which is far more accurate. The discussion of various neuroses is archaic and shows no understanding of dynamic principles or of recent advances made in this field. Aside from these defects the book is a useful and compact reference volume and serves as an excellent guide for the thorough examination of neurologic conditions.

H. W. N.

Thoughts of a Psychiatrist on the War and After. By WILLIAM ALANSON WHITE, M.D. Republished Essay. 28 pages; 26 × 18 cm. 1942. William Alanson White Psychiatric Foundation, Inc. (Originally copyrighted by Paul E. Hoeber in 1919). Price, \$1.50.

This is a small but very readable book. The author is one of the most brilliant thinkers and clear writers that American psychiatry has produced. In this book he traces the unconscious and instinctive forces, the mental mechanisms, of social organization and development. The psychological principles back of all conflict, including war, are clearly described. The problems and dangers confronting victor nations and peace-makers are outlined.

Although written during World War I, the principles described are so sound and so universal, it is difficult to believe that the author is not describing World War II. In the sense that the truth is always timely, this book is well worth reading now and throws considerable light on what to expect in the future.

H. W. N.

BOOKS RECEIVED

Books received during May are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Human Physiology. Ninth Edition. By E. H. STARLING, M.D., F.R.C.P., F.R.S. Edited and revised by C. LOVATT EVANS, D.Sc., F.R.C.P. 1155 pages; 24.5 × 16 cm. 1945. Lea & Febiger, Philadelphia. Price, \$10.00.

Cornell Conferences on Therapy. Volume 1. Edited by HARRY GOLD, M.D. 322 pages; 21 × 14 cm. The MacMillan Company, New York. 1946. Price, \$3.25.

- Agnosia, Apraxia, Aphasia.* 2nd Edition Revised. By J. M. NIELSEN, M.D., F.A.C.P., assisted by J. P. FITZGIBBON, M.D. 292 pages; 24 × 16 cm. 1946. Paul B. Hoeber, Inc., New York. Price, \$5.00.
- Principles and Practice of Tropical Medicine.* By L. EVERARD NAPIER, M.D., F.A.C.P., formerly Director of Tropical Medicine, Calcutta. 917 pages; 25.5 × 16.5 cm. 1946. The MacMillan Company, New York. Price, \$11.00.
- Electrocardiography.* Second Edition, Revised. By LOUIS N. KATZ, M.A., M.D., F.A.C.P. 883 pages; 26.5 × 17.5 cm. 1946. Lea & Febiger, Philadelphia. Price, \$12.00.
- Exercises in Electrocardiographic Interpretation.* Second Edition, Revised. By LOUIS N. KATZ, M.A., M.D., F.A.C.P. 288 pages; 26.5 × 17 cm. 1946. Lea & Febiger, Philadelphia. Price, \$6.00.
- The Diagnosis and Treatment of Pulmonary Tuberculosis.* By MOSES J. STONE, M.D., and PAUL DFAULT, M.D., F.A.C.P., with Foreword by HENRY D. CHADWICK, M.D. 325 pages; 20.5 × 14 cm. 1946. Lea & Febiger, Philadelphia.
- Carbohydrate Metabolism.* By SAMUEL SOSKIN, M.D., and RACHMIEL LEVINE, M.D. 315 pages; 25 × 17.5 cm. 1946. University of Chicago Press, Chicago. Price, \$6.00.
- Research and Regional Welfare.* Papers Presented at a Conference on Research at the University of North Carolina, Chapel Hill, May, 1945. Edited by ROBERT E. COKER, with foreword by LOUIS R. WILSON. 229 pages; 23.5 × 16 cm. 1946. University of North Carolina Press, Chapel Hill. Price, \$3.00.
- A History of Medicine.* By DOUGLAS GUTHRIE, M.D., F.R.C.S. with Introduction by SAMUEL C. HARVEY, M.D., F.A.C.S. 448 pages; 24 × 16 cm. 1946. J. B. Lippincott Company, Philadelphia, London. Price, \$6.00.
- New Human Embryology.* By BRADLEY M. PATTEN, Professor of Anatomy, University of Michigan Medical School. 776 pages; 26 × 17 cm. 1946. The Blakiston Company, Philadelphia. Price, \$7.00.
- The Vitamins in Medicine.* Second Edition. By FRANKLIN BICKNELL, D.M., M.R.C.P., and FREDERICK PRESCOTT, M.Sc., Ph.D. 916 pages; 23.5 × 16 cm. 1946. Grune & Stratton, Inc., New York. Price, \$12.00.
- Curarc Intocostrin.* Introduction by H. SIDNEY NEWCOMER, M.D. 292 pages; 21.5 × 14 cm. 1946. E. R. Squibb & Sons, New York.
- Oxford Loose-Leaf Medicine.* Supplements. 14 pamphlets. Oxford University Press, New York. 1946.



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Vanderbilt University, B.S., 1914; Johns Hopkins University School of Medicine, M.D., 1918; University of North Carolina, D.Sc. (Hon.), 1946.

Resident house officer, Johns Hopkins Hospital, 1919–20; assistant resident physician, Johns Hopkins Hospital, 1920–21; instructor in medicine, Johns Hopkins University School of Medicine, 1920–21; assistant and resident physician, Rockefeller Institute of Medical Research, 1922–24, traveling fellow (Europe), 1924–25; Associate Professor of Medicine, Vanderbilt University School of Medicine, 1924–28; Professor of Clinical Medicine, 1924–35; Professor of Medicine, Vanderbilt University School of Medicine, and Physician-in-Chief, Vanderbilt University Hospital 1935–. On leave of absence February 1, 1942—January 1, 1946.

Served as private and 1st lieutenant, Medical Corps, U.S. Army, A.E.F., 1917–18; lieutenant colonel, M.R.C., U.S. Army, 1940; colonel, M.C., U.S. Army, 1942; brigadier general, U.S.A., 1942–1946. Chief Consultant in Medicine to The Surgeon General, U.S. Army, 1942–46. D.S.M., 1945.

Fellow, American College of Physicians; Association of American Physicians; Board, Scientific Directors, International Health Division, Rockefeller Foundation; Society for Clinical Investigation; American Clinical and Climatological Association; American Association for the Advancement of Science; American Medical Association; Southern Medical Association; Phi Beta Kappa, Alpha Omega Alpha, Phi Delta Theta, Sigma Xi. Methodist.

Office: Vanderbilt University Hospital, Nashville 4, Tennessee; residence: White Bridge Pike, Nashville 5, Tennessee.

COLLEGE NEWS NOTES

NEW LIFE MEMBER

Dr. Leo E. Westcott, F.A.C.P., Kalamazoo, Mich., has become a Life Member of the American College of Physicians, under date of May 27, 1946.

GIFTS TO THE COLLEGE LIBRARY

The following gifts to the College Library are gratefully acknowledged:

- Victor W. Bergstrom, F.A.C.P., Binghamton, N. Y.—2 reprints
- Nathan Blumberg, F.A.C.P., Philadelphia, Pa.—1 reprint
- Mortimer J. Cantor, (Associate), Brooklyn, N. Y.—1 reprint
- Oscar G. Costa-Mandry, F.A.C.P., San Juan, P. R.—2 reprints
- C. Wesley Eisele, F.A.C.P., Chicago, Ill.—1 reprint
- Norbert Enzer, F.A.C.P., Milwaukee, Wis.—1 reprint
- Irving Greenfield, F.A.C.P., New York, N. Y.—1 reprint
- Percy G. Hamlin, (Associate), Santa Barbara, Calif.—5 reprints
- Chester S. Keefer, F.A.C.P., Boston, Mass.—7 reprints
- John E. Leach, F.A.C.P., New York, N. Y.—1 reprint
- Arthur G. Lueck, (Associate), Great Lakes, Ill.—1 reprint
- Frederick W. Niehaus, F.A.C.P., Omaha, Nebr.—3 reprints
- Hilton S. Read, F.A.C.P., Ventnor City, N. J.—3 reprints
- Bernard Seligman, F.A.C.P., Brooklyn, N. Y.—3 reprints
- Ralph L. Shanno, F.A.C.P., Forty Fort, Pa.—2 reprints
- Jacob Jesse Singer, F.A.C.P., Beverly Hills, Calif.—1 reprint
- Frederick R. Weedon, (Associate), Jamestown, N. Y.—2 reprints
- Burton L. Zohman, F.A.C.P., Brooklyn, N. Y.—5 reprints

Dr. Leland P. Shipp, (Associate), Battle Creek, Mich., has donated the following books to the College Library:

"Lectures on the Principles and Practice of Physic," as delivered at King's College, London, by Thomas Watson, M.D. (Revised, with additions by D. Francis Comdie, M.D.), published by Blanchard and Lea, Philadelphia, 1852.

"A Text-book of Practical Medicine," Vol. I, by Felix von Niemeyer, M.D., George H. Humphreys, M.D., and Charles E. Hackley, M.D., published by D. Appleton and Company, New York, 1871.

"A Treatise on the Practice of Medicine," by George B. Wood, M.D., Fifth Edition, Vol. II, published by J. B. Lippincott and Co., Philadelphia, 1858.

MEDICAL CONSULTANTS APPOINTED TO ASSIST IN GRADUATE TRAINING PROGRAM, MEDICAL CORPS, U. S. NAVY

Vice Admiral Ross T. McIntire, (MC), U.S.N., F.A.C.P., Surgeon General of the Navy has announced the appointment of 16 members of the Reserve Consultants Board to the Bureau of Medicine and Surgery. All are outstanding specialists in their respective fields. They will assist the Bureau in furthering the graduate training program, which, in addition to increasing the professional proficiency and improving the standards of medical practice, is designed to afford Naval medical officers the opportunity to train in medical specialties and to qualify for American Board certification, Fellowship in one of the American Colleges, or other marks of distinction in the same manner as doctors engaged in civilian practice.

Among those appointed are the following:

Captain F. J. Braceland, (MC), U.S.N.R., F.A.C.P., Secretary, American Board of Psychiatry and Neurology.

Commodore Alphonse McMahon, (MC), U.S.N.R., F.A.C.P., Associate Professor of Medicine, St. Louis University School of Medicine.

Dr. J. Roscoe Miller, F.A.C.P., Dean and Associate Professor of Medicine, Northwestern University School of Medicine.

1947, ANNUAL SESSION, AMERICAN COLLEGE OF PHYSICIANS, CHICAGO,
April 28-May 2.

The 28th Annual Session of the College will be held at the Palmer House, Chicago, Ill., from Monday through Friday, April 28-May 2, 1947. Dr. LeRoy H. Sloan, Chicago, will be General Chairman, in charge of local arrangements. He has already started the appointment of committees and an enthusiastic group are working on the preparation. Dr. Sloan will be responsible, not only for local arrangements, but for the program of clinics and panel discussions. Both of these programs were inadequate to accommodate the large numbers attending the Annual Sessions in Philadelphia in 1946. Therefore, adequate extension of these programs is being planned. Dr. David P. Barr, of New York, President of the College, is preparing the program of General Sessions and Morning Lectures. Watch these columns for further announcements during the months to come.

THE AMERICAN COLLEGE OF PHYSICIANS COMMITTEE ON NOMINATIONS 1946-1947

In accordance with provisions of the By-Laws, President David P. Barr, on May 21, 1946, appointed the following Committee on Nominations, for 1946-1947, whose duties shall be to nominate candidates for elective offices and for the Board of Regents and Board of Governors. The nominations for the elective officers will be published at least one month in advance of the Annual Business Meeting in 1947, at Chicago. Nominations of Regents and Governors are presented at the Business Meeting without prior publication, but no nominations by this Committee preclude nominations that may be made from the floor of the Meeting:

James J. Waring (Regent), Denver—Chairman
George F. Strong (Regent), Vancouver
Ralph Kinsella (Governor), St. Louis
Asa L. Lincoln (Governor), New York
Jonathan Meakins (Fellow-at-large), Montreal

REPORTS ON RECENT A.C.P. POSTGRADUATE COURSES

Course No. 5

Course No. 5 Metabolism and Nutrition, was conducted at the Nutrition Clinic of the Hillman Hospital, Birmingham, Ala., June 3-8, 1946, under the Directorship of Dr. Tom D. Spies, F.A.C.P. This was the first course the College had ever sponsored in this particular field. The class purposely was limited in size to twelve registrants. An average of four patients per hour were shown during the clinical sessions. During the teaching sessions minute details were entered into, with explanations of their methods of diagnosing nutritional deficiency diseases and proper therapeutic measures. Question and answer periods were utilized to great advantage. Two afternoons were devoted to field studies, giving the doctors an opportunity to study patients in their own homes and to observe the economic conditions under which they lived. To see the patients in their home surroundings did much to establish a

personal interest in the patients who were shown in the clinical demonstrations. Many of the registrants had never been to Alabama before and had little appreciation of the plight of the South's poor. The patients are already accustomed to the Hillman Clinic social workers coming to their homes, and, therefore, there was no difficulty in having the registrants examine all members of the family, right in the home.

This week of intensive clinical instruction presented a unique opportunity to learn how to cope with the problem of nutritive failure.

Course No. 10

Course No. 10, Internal Medicine, was conducted June 17-28, 1946, at the University of California Medical School and Medical Center, San Francisco, under the Directorship of Dr. Stacy R. Mettier, F.A.C.P. The course was purposely arranged for the two weeks preceding the Annual Meeting of the American Medical Association, thus to give an opportunity to physicians, not only to take the course, but to remain for the A.M.A. Meeting. One hundred and thirteen were registered in the course. At the time of preparation of this news item, the course is just getting under way and details are not ready for publication. The College is gratified with the exceedingly great interest displayed in the course and the fact that College courses are being so well established along the West Coast. The registrants are from all parts of the United States and Canada, showing the importance that they have attached to this exceedingly fine course given by outstanding teachers from the University of California.

INDEX AND SUMMARY OF REGISTRATIONS, SPRING COURSES, 1946

No.	Title	Institution	Director	Dates
1-A.	Clinical Allergy	Massachusetts General Hospital, Boston, Mass.	Dr. Francis R. Rackemann	March 4-9.
1-B.	Clinical Allergy	Massachusetts General Hospital, Boston, Mass.	Dr. Francis R. Rackemann	April 8-13.
1-C.	Clinical Allergy	Massachusetts General Hospital, Boston, Mass.	Dr. Francis R. Rackemann	July 8-13.
2.	General Medicine	Jefferson Medical College, Philadelphia, Pa.	Dr. Hobart A. Reimann	March 18-23.
3.	General Medicine	University of Texas, School of Medicine, Galveston, Tex.	Dr. Charles T. Stone	March 25-30.
4.	Internal Medicine	Massachusetts General Hospital, Boston, Mass.	Dr. James H. Means	April 1-19.
5.	Metabolism and Nutrition	Nutrition Clinic, Hillman Hospital, Birmingham, Ala.	Dr. Tom D. Spies	June 3-8.
6.	General Medicine	Emory University, School of Medicine, Atlanta, Ga.	Dr. James E. Paullin	April 22-27.
7.	Gastro-enterology	Graduate Hospital, Philadelphia, Pa.	Dr. Henry L. Bockus	April 29-May 4.
8.	Cardiology	Philadelphia General Hospital and the Woman's College of Pennsylvania, Philadelphia, Pa.	Dr. William G. Leaman	May 6-11.
9.	Thoracic Diseases	Department of Postgraduate Medicine, University of Michigan Medical School, Ann Arbor, Mich.	Dr. John Alexander	May 6-11.
10.	Internal Medicine	University of California, Medical School and Medical Center, San Francisco, Calif.	Dr. Stacy R. Mettier	June 17-28.

No.	Fellows	Associates	Non-members	TOTAL	Army	Navy	U.S.P.H.S.	Civilians
1-A.	4	2	0	6	1	0	0	5
1-B.	4	2	0	6	0	0	0	6
1-C.	4	2	0	6	1	1	0	4
2.	35	14	52	101	35	8	6	52
3.	9	7	38	54	9	24	3	18
4.	50	21	11	82	25	4	2	51
5.	4	2	6	12	1	0	3	8
6.	13	7	5	25	7	1	0	17
7.	50	19	9	78	7	3	1	67
8.	113	38	8	159	16	9	0	134
9.	12	15	15	42	7	3	1	31
10.	36	22	55	113	33	11	2	67
	<u>334</u>	<u>151</u>	<u>199</u>	<u>684</u>	<u>142</u>	<u>64</u>	<u>18</u>	<u>460</u>

A. C. P. POSTGRADUATE COURSES, AUTUMN, 1946
(Tentative; not yet final)

The following schedule is still tentative, owing to a few factors requiring further adjustment. At this date (June 19, 1946) the schedule appears to be reasonably final, but some changes have been made recently. Three courses previously announced for the Autumn have been deferred until the Spring of 1947: to wit, a two weeks' course in Internal Medicine, with some emphasis on metabolic disorders, under the direction of Dr. M. A. Blankenhorn, University of Cincinnati; a one week course in Physical Medicine, under the direction of Dr. George Morris Piersol, University of Pennsylvania, Philadelphia; a one week course in Cardiology under Dr. J. Roscoe Miller, Northwestern University, Chicago; a one week course in Tissue Growth and Tumors under Dr. Stanley Reimann at the Lankenau Hospital, Philadelphia.

Dates	Title	Director	Location
Sept. 2-14	INTERNAL MEDICINE	Dr. R. R. Snowden	Pittsburgh, Pa.
" 23-28	PSYCHOSOMATIC MEDICINE	Dr. Franklin Ebaugh	Denver, Colo.
Oct. 7-19	INTERNAL MEDICINE	Dr. Homer Rush	Portland, Ore.
" 14-18	CLINICAL NEUROLOGY	Dr. Bernard Alpers	Philadelphia, Pa.
" 21-26	HEMATOLOGY	Dr. Charles A. Doan	Columbus, Ohio
" 21 to			
Nov. 1	INTERNAL MEDICINE	Dr. Wallace M. Yater	Washington, D. C.
Nov. 4-9	ALLERGY	Dr. Robert A. Cooke	New York, N. Y.
" 4-9	CARDIOLOGY	Dr. Paul White	Boston, Mass.
" 11-16	GASTRO-ENTEROLOGY	Dr. Walter L. Palmer	Chicago, Ill.
" 18-23	INTERNAL MEDICINE	Dr. Joseph Hayman	Cleveland, Ohio
" 25 to			
Dec. 6	INTERNAL MEDICINE	Dr. J. C. Meakins	Montreal, Que.
Dec. 2-7	CHEMOTHERAPY	Dr. W. Barry Wood, Jr.	St. Louis, Mo.
" 2-7	CARDIOLOGY	Dr. Frank Wilson	Ann Arbor, Mich.

Detailed bulletins of each course and registration forms will be mailed to all members of the American College of Physicians on or before August 1; also to non-member physicians who have requested being placed on the mailing list.

Fees: (1) Courses in which the maximal registration is restricted to 15 or less, \$40.00 per week to members; \$80.00 per week to non-members. (2) Courses in which the maximal registration permits more than 15 registrants, \$20.00 per week to members; \$40.00 per week to non-members.

Inquiries should be addressed to E. R. Loveland, Executive Secretary, American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

Dr. Hugh J. Morgan, F.A.C.P., President-Elect of the College, Nashville, Tenn., was recently awarded the Distinguished Service Medal. His citation was as follows, "as chief consultant in medicine, Office of the Surgeon General, from February, 1942, to August, 1945, he performed exceptionally meritorious service. Through his untiring efforts the best medical talent in the country was mobilized for service with the Army. Demonstrating marked ability, initiative and judgment in formulating professional policies in the field of medicine and in the assignment of the highest type medical personnel as consultants and chiefs of services, he contributed to the excellent type of medical care received by seriously sick enlisted men and officers. He implemented the procurement of the latest and best supplies and equipment obtainable in order to further alleviate suffering."

Dr. Rafael Rodriguez-Molina, F.A.C.P., San Juan, P. R., was awarded recently the Army Commendation Ribbon, his citation reading as follows: "The Army Commendation Ribbon is hereby awarded for commendable service from May 22, 1942 to February 12, 1946, as assistant chief and chief of the medical service, 161st General Hospital, A.P.O. 851, U. S. Army. During this period Major Rodriguez-Molina displayed outstanding efficiency and devotion to duty. His professional skill coupled with exceptional tact and keen knowledge of the psychology and customs of Puerto Ricans contributed greatly to the accomplishment of the medical mission of this department. His accomplishments reflect great credit on him and on the military service."

Col. Harold C. Lueth, (MC), AUS, F.A.C.P., has received the Army Commendation Ribbon, his citation reading as follows: "During World War II the Medical Department carried out its mission with outstanding success. This achievement was made possible only through the combined efforts of all Medical Department personnel. Your service with the Medical Department has been exceptional when compared with others of the same grade of similar position, and I wish to commend you for your outstanding contribution as liaison officer between the Office of the Surgeon General and the American Medical Association from March 15, 1942 to February 25, 1945."

Lieut. Col. Charles C. Verstandig, (MC), AUS, (Associate), New Haven, Conn., was recently awarded the Army Commendation Ribbon. His citation was as follows: "During World War II the Medical Department carried out its mission with outstanding success. This achievement was made possible only through the combined efforts of all Medical Department personnel. Your service with the Medical Department has been exceptional when compared with others of the same grade of similar position, and I wish to commend you for your outstanding contribution as medical director, Armed Forces Recruiting and Induction Station, New Haven, from March 1, 1943 to December 31, 1945."

Col. Cleve C. Odom, (MC), USA, F.A.C.P., has been awarded the Legion of Merit. His citation was as follows: "Colonel Cleve C. Odom, Medical Corps, Army of the United States, while serving as Commanding Officer of Mason General Hospital, distinguished himself through outstanding service. Colonel Odom expanded Mason General Hospital from a 1,320 to a 3,032 bed hospital during his tenure of command and provided instruction of the highest quality for medical officers and nurses undergoing instruction in the School of Military Neuropsychiatry operated at this station. Through his broad experience in neuropsychiatry and hospital administration, untiring efforts, remarkable initiative and enthusiastic and virile leadership, Mason General

Hospital attained a prominent place in military neuropsychiatry and administered the best of care and treatment to the neuropsychiatric patients of the Army. His cumulative achievements reflect great credit on himself and the medical corps."

SURPLUS ARMY HOSPITALS RELEASED TO VETERANS ADMINISTRATION

The Army's great general hospitals, built to the latest medical and surgical standards for the care and treatment of its wounded and sick during the war, are being released as rapidly as the decrease in the patient load justifies and offered first to the Veterans Administration for its rapidly expanding program for medical care for veterans.

The transfers have been made as part of the Army's comprehensive plan, devised before hostilities had ceased, to effect a smooth transition when responsibilities for the care of the sick and wounded were transferred from the Army to the Veterans Administration.

The War Department program is being carried out through close coöperation between Major General Norman T. Kirk, F.A.C.P., The Surgeon General, and Dr. Paul R. Hawley, F.A.C.P., Medical Director of the Veterans Administration, who before retirement from the Army as a Major General, was Chief Surgeon in the European Theatre of Operations.

Already 11 hospitals have been transferred completely to the Veterans Administration, according to a report from Surgeon General Kirk.

RHEUMATIC FEVER COUNCIL RECEIVES INITIAL FUND OF \$50,000

At Atlantic City on May 29, it was announced that the American Legion had presented the American Council on Rheumatic Fever with a check for \$50,000 to start a nation-wide campaign to raise the minimum of \$5,000,000 a year to combat this disease. The presentation was made by Dr. Leonard G. Rowntree, F.A.C.P., Philadelphia, who is chief medical adviser to the American Legion. The gift was accepted by Dr. Roy W. Scott, F.A.C.P., Cleveland, who is President of the American Heart Association, which was the organizer of this Council on Rheumatic Fever. The American College of Physicians has donated \$1,000 to the Fund.

NEW JERSEY MEMBERS HOLD MEETING AT ATLANTIC CITY, MAY 22

Fellows and Associates of the American College of Physicians of New Jersey held a luncheon meeting at the Hotel Traymore, Atlantic City, May 22, during the Annual meeting of the New Jersey State Medical Society. Arrangements were conducted by Dr. Johannes Pessel, F.A.C.P., Trenton. Dr. George H. Lathrope, F.A.C.P., Governor for New Jersey, presided. Dr. William D. Stroud, F.A.C.P., Philadelphia, Treasurer of the College, and Mr. E. R. Loveland, Executive Secretary of the College, addressed the group about College matters. Fifty-four members were in attendance.

WESTERN MICHIGAN MEMBERS HOLD SECOND REGIONAL MEETING

Members of the American College of Physicians in Western Michigan, as announced recently in these columns, have organized for the conduct of three or more scientific and social regional meetings each year. The second such meeting was held at the Percy Jones General Hospital, May 1, 1946, with 31 members in attendance. Dr. William N. LeFevre, Muskegon, is the Secretary.

COLLEGE NEWS FROM PUERTO RICO

During the annual meeting of the Puerto Rico Medical Association held during December 1945, the following members of the American College of Physicians took active part in the meeting:

Dr. Franklin L. Hanger, Jr., F.A.C.P., of Columbia University, New York City.

Dr. Henry L. Bockus, F.A.C.P., of the University of Pennsylvania, Philadelphia.

Dr. Ramón M. Suárez, F.A.C.P., in coöperation with Dr. Tom Spies, F.A.C.P., Birmingham, Ala., talked on the treatment of macrocytic anemia with folic acid.

Dr. Rafael Rodríguez-Molina, F.A.C.P., Major, A.U.S., also took active part in the meeting.

Dr. Federico Hernández, F.A.C.P., of the School of Tropical Medicine was invited by Tulane University to give a short course during a period of two months. Dr. Hernández returned from New Orleans during the month of March.

Dr. O. Costa Mandry, F.A.C.P., of the Health Department of Puerto Rico, was invited by the Rockefeller Foundation to coöperate in the establishment of a public health laboratory in the Dominican Republic. During the second week of January Dr. Costa Mandry visited the Dominican Republic to outline plans for the establishment of this laboratory.

During the month of November the members of the College in Puerto Rico gave an informal luncheon to Dr. R. Rodríguez-Molina on account of his promotion in the Army from Captain to Major.

Dr. Luis M. Morales, F.A.C.P., of San Juan, was appointed during the month of December President of the Puerto Rico Medical Association.

Dr. Ramón M. Suárez, College Governor of the District of Puerto Rico, left at the beginning of April for the Annual Session of the American College of Physicians at Philadelphia to present a paper on the treatment of sprue by folic acid.

Dr. C. C. Carpenter, Dean of The Bowman Gray School of Medicine of Wake Forest College, recently announced the gift of \$125,000 from Mr. Bowman Gray, Jr., matching a similar amount recently given to the school by his brother, Mr. Gordon Gray. Both of these gifts are unrestricted in their use.

A department of Preventive Medicine has been organized, and Dr. Thomas T. Mackie of New York has been elected Professor of Preventive Medicine and Chairman of the Division of Medicine.

Dr. John H. Ferguson, Professor of Physiology at the University of North Carolina School of Medicine, addressed the Bowman Gray Medical Society on April 15, 1946. His subject was: "Blood Coagulation and Modern Clinical Applications."

Dr. Edward C. Reifenstein, F.A.C.P., has been honored by the establishment of the Dr. Edward C. Reifenstein Lectureship in Medicine at Syracuse University College of Medicine by the family of Dr. Ellery G. Allen. Dr. Reifenstein became professor emeritus of medicine on July 1, 1940, but has continued as chairman of the department during the war years.

The first lecture was given by Dr. Edgar V. Allen, F.A.C.P., associate professor of medicine at the University of Minnesota, Mayo Foundation, Rochester, April 8, his subject being, "The Challenge of Intravascular Thrombosis."

Dr. Franklin B. Bogart, F.A.C.P., Chattanooga, Tenn., has been elected president-elect of the Tennessee State Medical Association.

Dr. Robert F. Loeb, F.A.C.P., professor of medicine at Columbia University College of Physicians and Surgeons, is one of twenty-nine leaders in American Science recently elected to membership in the National Academy of Science.

Among the speakers at the 180th annual meeting of the Medical Society of New Jersey on May 22, 1946, in the Section of Gastro-enterology and Proctology were Dr. Manfred Kraemer, F.A.C.P., Newark, who spoke on "Intestinal Parasitism in an Army Hospital," and Dr. Louis L. Perkel, F.A.C.P., Jersey City, who spoke on "Esophageal Hiatus Hernia." The officers elected by the section for the coming year were Dr. Louis L. Perkel, F.A.C.P., and Dr. Sigurd W. Johnson, F.A.C.P., Passaic, chairman and secretary, respectively.

The Medical Society of Virginia will hold its annual meeting at Virginia Beach, October 14-16, 1946. Dr. A. B. Hodges, F.A.C.P., will be the chairman of the meeting.

Rear Admiral Kent C. Melhorn, F.A.C.P., (MC), U.S.N., delivered the commencement address before the University of Virginia Department of Medicine on March 20.

Dr. Eugene M. Landis, F.A.C.P., Professor of Physiology at Harvard Medical School, gave the annual Alpha Omega Alpha address, April 19, on "Venous Pressure and Cardiac Failure in the Laboratory and Clinic."

Dr. L. E. January (Associate), was recently separated from the Medical Corps, AUS, as a Lieutenant Colonel, and has been appointed assistant professor of internal medicine at the State University of Iowa.

Dr. George F. Lull, F.A.C.P., Chicago, addressed the first Rocky Mountain Regional Conference on Medical Service and Public Relations at Denver on June 5 on the subject, "Problems of the Returning Medical Officer."

Dr. Arthur C. Christie, F.A.C.P., Washington, D. C., delivered the George W. Holmes annual lecture before the annual meeting of the New England Roentgen Ray Society, at Boston, on May 17, his subject being, "The First Fifty Years of Radiology: The Elements Which Have Contributed to Its Growth as a Great Medical Specialty."

Dr. Stockton Kimball, F.A.C.P., who has been a member of the faculty of the University of Buffalo School of Medicine for many years, was recently appointed dean of the medical school to succeed Dr. Edward W. Koch, deceased.

The forty-seventh annual meeting of the American Therapeutic Society at Atlantic City, May 11-12, 1946, was addressed by the following members of the College:

Dr. Oscar B. Hunter, Jr., F.A.C.P., Washington, D.C., "Correlation of Laboratory Findings with Therapy in Epidemic Hepatitis;"

Dr. David I. Macht, F.A.C.P., Baltimore, Md., "An Experimental Approach to the Therapy of Pemphigus;"

Dr. Daniel L. Sexton, F.A.C.P., St. Louis, Mo., "Thiouracil—Clinical Evaluation Following Two and One Half Years' Experience;"

Dr. Francis M. Pottenger, F.A.C.P., Monrovia, Calif., "Difficulties in Physical Examination of the Chest;"

Dr. David Salkin, F.A.C.P., Hopemont, W. Va., "Postmortem Pneumothorax;"

Dr. Nathan S. Davis, III, F.A.C.P., Chicago, Ill., "The Treatment of Hypertensive Cardiovascular Renal Disease with Ascorbic Acid, Riboflavin and Vitamin B Complex."

Dr. Stanley P. Reimann, F.A.C.P., Philadelphia, Pa., addressed the Ohio State Medical Association at its one hundredth anniversary meeting at Columbus, May 7-9, on "Present Status of Cancer Research."

The Southern Medical Association announces its next annual meeting at Miami, Fla., November 4-7, 1946.

Brigadier General George R. Callender, F.A.C.P., (MC), U.S.A., Commandant of the Medical Department Professional Service Schools, Washington, D. C., was recently awarded the Richard Pearson Strong Paladium Medal of the American Foundation for Tropical Medicine. This medal, including an honorarium of \$500, is given by the Winthrop Chemical Company, New York.

Dr. George Albert Gray, F.A.C.P., formerly of Abilene, Tex., retired from the Army with the rank of Lieutenant Colonel recently and has been appointed Director of the San Angelo-Tom Green County Health Unit, San Angelo, Tex.

Dr. Merritt Henry Stiles, F.A.C.P., formerly of Philadelphia, was retired from the Army with the rank of Lieutenant Colonel early this year and is established in practice at 1070 Paulsen Medical-Dental Bldg., Spokane, Wash.

Dr. Herbert Pollack, F.A.C.P., who recently has been serving as Chief Medical Consultant in the European Theater, has retired from the Army with the rank of Colonel and returned to civilian practice at 45 E. 66th St., New York City.

Dr. Hugh R. Leavell, F.A.C.P., for many years Director of Public Health, Louisville, Ky., served from November, 1944, to December, 1945, in the USPHS (R). He has now accepted an appointment as Assistant Director of the Division for the Medical Sciences of the Rockefeller Foundation, New York City, and is assigned to Undergraduate Medical Education in Preventive Medicine.

Dr. Ralph Frederick Schneider (Associate), retired from the United States Naval Reserve during April, is now associated with the Medical Department of the Standard Oil Company, 30 Rockefeller Plaza, New York City. On May 28 he left for South America, where, in conjunction with American Board members in Surgery and Obstetrics, he will participate in a teaching and reorganization program in the hospitals of the Standard Oil Company affiliates.

Dr. Henry B. Gwynn, F.A.C.P., who since 1943 has been Associate Clinical Professor of Medicine at Georgetown University School of Medicine, Washington, D. C., has removed to Mobile, Ala., where he has established an office at 751 Government St.

Dr. George S. Grier, III (Associate), has recently completed a Fellowship in Pathology at the Medical College of Virginia, Richmond, and on July 1 opened his office at 130 26th St., Newport News, Va.

In the May issue of this journal it was inadvertently published that Dr. Marsh McCall, F.A.C.P., had recently retired from the Army with the rank of Lieutenant Colonel, whereas later records disclosed he was separated from duty with the rank of Colonel.

Dr. James E. Paullin, F.A.C.P., Atlanta, presented the dedication address at a meeting of the Fulton County Medical Society, at the Atlanta Academy of Medicine on April 4. It was the occasion of the dedication of the auditorium of the Fulton County Academy of Medicine to Dr. Abner Wellborn Calhoun.

Dr. Joseph C. Edwards, F.A.C.P., Lt. Col., (MC), AUS, with the 21st General Hospital, and now Instructor in Medicine at Washington University, St. Louis, Mo., was awarded the Legion of Merit with a Citation for clinical research during the war, in the Mediterranean and the E. T. O.

Dr. George H. Houck, F.A.C.P., recently retired from the Army of the United States, has accepted an appointment as director of student health, Stanford University.

Dr. Francis M. Pottenger, Sr., F.A.C.P., Monrovia, Calif., has been named to the newly created office of president emeritus of the Los Angeles County Tuberculosis and Health Association. Dr. Pottenger was one of the founders of this Society.

Dr. Cyril M. MacBryde, F.A.C.P., formerly of St. Louis, is now assistant clinical professor of medicine at the University of Southern California School of Medicine, Los Angeles.

The Idaho State Medical Association's annual meeting at Boise, June 17-20, was addressed by Dr. James J. Waring, F.A.C.P., Denver, Colo., on "Various Aspects of Tuberculosis," and by Dr. Ward Darley, Jr., F.A.C.P., Denver, Colo., on "Diagnosis of Rheumatic Fever and Rheumatic Heart Disease."

Dr. Chester S. Keefer, F.A.C.P., Boston, addressed the 92nd session of the Maine Medical Association, at Poland Spring, June 23-25, on streptomycin.

Brigadier General James S. Simmons, (MC), USA, F.A.C.P., Chief of the Preventive Medicine Service, Office of The Surgeon General, was awarded the honorary degree of Doctor of Science from the University of North Carolina, at Chapel Hill, recently.

General Simmons will assume duties as Dean of the Harvard School of Public Health on July 1, when he retires from the Regular Army.

Dr. Harold J. Jeghers, F.A.C.P., Boston, Massachusetts, has been appointed Professor and Director of the Department of Medicine at the Georgetown University School of Medicine and physician-in-chief of the Georgetown University Hospital. The appointment became effective July 1, 1946. Dr. Jeghers has been associated with the Boston University School of Medicine and Boston City Hospital since 1935 and with the Evans Memorial Hospital since 1939.

Dr. Howard Wakefield, F.A.C.P., and Dr. S. W. McArthur, both of Chicago, addressed the Racine County Medical Society, at Racine, Wis., April 18, 1946, on "The Association of Gall Bladder Disease and Heart Disease: Clinical and Experimental Observations."

Dr. Lee D. Cady, F.A.C.P., who formerly served in the Army as a Colonel in the Medical Corps, is now the Branch Medical Director of the U. S. Veterans Administration, representing Texas, Louisiana and Mississippi. He is located in the Mercantile Bank Bldg., Dallas, Tex.

At the Third Annual Meeting of the American Society for Research in Psychosomatic Problems, at Hotel Pennsylvania, New York City, May 11-12, 1946, Dr. Edward Weiss, F.A.C.P., Philadelphia, was elected President, and Dr. William Dock, F.A.C.P., New York City, and Dr. Leonard G. Rowntree, F.A.C.P., of Philadelphia, were elected to the Council.

Dr. Harold G. Trimble, F.A.C.P., was the dinner speaker at the meeting of the Oregon Tuberculosis Association, at Portland, during May.

Dr. Hyman I. Goldstein, Associate, Camden, N. J., addressed the American Association of the History of Medicine at its 19th Annual Meeting, Atlantic City, May 27, 1946, on "The History of Medical Education and of Some Medical Men, in New Jersey."

The American Clinical and Climatological Society will meet at Hershey, Pa., October 21-23, 1946.

Dr. Daniel L. Sexton, F.A.C.P., St. Louis, has been elected Vice President of the Missouri State Medical Association.

Dr. Roy C. Mitchell, F.A.C.P., Mount Airy, has been elected President of the Eighth District County Medical Society of North Carolina.

RETIREMENTS FROM SERVICE

Since the last publication of this journal, the following members of the College have been reported retired or on terminal leave (to June 13, 1946 inclusive).

Horst A. Agerty, Merion Station, Pa. (Capt., MC, AUS)
 John J. Archinard, New Orleans, La. (Lt. Col., MC, AUS)
 Gerald S. Backenstoe, Emmaus, Pa. (Major, MC, AUS)
 George N. Barry, Oklahoma City, Okla. (Lt. Comdr., MC, USNR)
 M. Meredith Baumgartner, Janesville, Wis. (Comdr., MC, USNR)
 Joseph C. Bell, Louisville, Ky. (Lt. Col., MC, AUS)
 Abraham Becker, Detroit, Mich. (Major, MC, AUS)
 Lawrence H. Beizer, Rochester, Minn. (Lt. Col., MC, AUS)
 Charles A. Bohnengel, New York, N. Y. (Lt. Col., MC, AUS)
 Donald W. Bortz, Cleveland, Ohio (Lt., MC, USNR)
 Samuel R. Brownstein, New York, N. Y. (Major, MC, AUS)
 Harold J. Brumm, St. Joseph, Mo. (Lt. Comdr., MC, USNR)
 Samuel Candel, Brooklyn, N. Y. (Comdr., MC, USNR)
 Manley J. Capron, Battle Creek, Mich. (Capt., MC, USNR)

Herman M. Chesluk, Detroit, Mich. (Capt., MC, AUS)
George R. Crisler, Winter Park, Fla. (Major, MC, AUS)
Haydn H. Cutler, Houston, Tex. (Lt. Col., MC, AUS)
Mahlon H. Delp, Kansas City, Kan. (Col., MC, AUS)
John S. Denholm, Burlington, N. C. (Col., MC, AUS)
George P. Denny, Boston, Mass. (Col., MC, AUS)
Frederick W. Fitz, Chicago, Ill. (Lt. Col., MC, AUS)
Ralph G. Fleming, Durham, N. C. (Major, MC, AUS)
Robert F. Foster, Seattle, Wash. (Major, MC, AUS)
A. James French, Ann Arbor, Mich. (Lt. Col., MC, AUS)
Franklin W. Fry, Hempstead, N. Y. (Capt., MC, AUS)
Joseph J. Furlong, Milwaukee, Wis. (Lt. Comdr., MC, USNR)
Cleo R. Gatley, Pontiac, Mich. (Major, MC, AUS)
James T. J. Geddis, New York, N. Y. (Major, MC, AUS)
Hermon C. Gordinier, Troy, N. Y. (Lt. Col., MC, AUS)
George A. Gray, Abilene, Tex. (Lt. Col., MC, AUS)
Edward D. Greenwood, Topeka, Kan. (Major, MC, AUS)
William H. Grishaw, Los Angeles, Calif. (Major, MC, AUS)
Morris B. Guthrie, Columbus, Ohio (Col., MC, AUS)
Russell B. Hanford, Spokane, Wash. (Lt. Col., MC, AUS)
Thomas J. Hanlon, St. Louis, Mo. (Major, MC, AUS)
John Harvey, Lexington, Ky. (Lt. Col., MC, AUS)
William R. Hewitt, Tucson, Ariz. (Lt. Col., MC, AUS)
A. Parker Hitchens, Philadelphia, Pa. (Lt. Col., MC, USA)
Edward D. Hoedemaker, Seattle, Wash. (Lt. Comdr., MC, USNR)
A. Gerson Hollander, Brooklyn, N. Y. (Lt. Col., MC, AUS)
Kendall B. Holmes, Fresno, Calif. (Major, MC, AUS)
J. Morris Horn, Fort Worth, Tex. (Major, MC, AUS)
Lewis E. January, Iowa City, Iowa (Lt. Col., MC, AUS)
Henry J. John, Cleveland, Ohio (Lt. Col., MC, AUS)
Louis Krause, Baltimore, Md. (Lt. Col., MC, AUS)
L. Rush Lambert, Fairmont, W. Va. (Col., MC, AUS)
Thomas A. Lebbetter, Yarnouth, N. S., Can. (Col., RCAMC)
Clarence W. LeDoux, Baltimore, Md. (Capt., MC, AUS)
Henry J. Lehnhoff, Jr., Rochester, Minn. (Lt. Col., MC, AUS)
Frederick Lemere, Seattle, Wash. (Lt. Col., MC, AUS)
Victor F. Lief, Far Rockaway, N. Y. (Lt. Col., MC, AUS)
Wallace W. Lindahl, Rochester, Minn. (Major, MC, AUS)
Edward A. Marshall, Cleveland, Ohio (Lt. Col., MC, AUS)
John R. Shannon Mays, Baltimore, Md. (Lt. Col., MC, AUS)
Donald McCarthy, Minneapolis, Minn. (Capt., MC, USNR)
William U. McClenahan, Philadelphia, Pa. (Major, MC, AUS)
Leo J. Meienberg, Portland, Ore. (Lt. Comdr., MC, USNR)
Nathan T. Milliken, Hanover, N. H. (Lt. Col., MC, AUS)
Fred S. Modern, Los Angeles, Calif. (Lt. Comdr., MC, USNR)
Clifford K. Murray, Ventnor, N. J. (Lt. Comdr., MC, USNR)
Alonzo Y. Olsen, Los Angeles, Calif. (Major, MC, AUS)
John R. Osborne, Middletown, N. Y. (Comdr., MC, USNR)
Arthur L. Osterman, Wheeling, W. Va. (Capt., MC, USNR)
Frank Perlman, Portland, Ore. (Lt. Col., MC, AUS)
Herbert Pollack, New York, N. Y. (Col., MC, AUS)
Everett B. Poole, Greenville, S. C. (Col., MC, AUS)
Hans P. Popper, Chicago, Ill. (Major, MC, AUS)
William W. Priddle, Toronto, Ont., Can. (Major, RCAMC)

David E. Quinn, Livermore, Calif. (Col., MC, AUS)
 David R. Sacks, San Antonio, Tex. (Lt. Col., MC, AUS)
 Charles H. Scheifley, Rochester, Minn. (Capt., MC, AUS)
 Sidney Scherlis, Baltimore, Md. (Major, MC, AUS)
 Ralph F. Schneider, New York, N. Y. (Lt., MC, USNR)
 Leon Schwartz, Philadelphia, Pa. (Surgeon, USPHS (R))
 Fred F. Senerchia, Jr., Elizabeth, N. J. (Col., MC, AUS)
 Richard M. Shick, Rochester, Minn. (Lt. Comdr., MC, USNR)
 James J. Short, New York, N. Y., (Capt., MC, USNR)
 Jacob J. Silverman, Staten Island, N. Y. (Major, MC, AUS)
 Robert L. Smith, Jr., Rochester, Minn. (Major, MC, AUS)
 Dale C. Stahle, Harrisburg, Pa. (Major, MC, AUS)
 Edson H. Steele, Los Angeles, Calif. (Comdr., MC, USNR)
 Israel Steinberg, New York, N. Y. (Comdr., MC, USNR)
 Morris F. Steinberg, New York, N. Y. (Capt., MC, AUS)
 Merritt H. Stiles, Philadelphia, Pa. (Lt. Col., MC, AUS)
 Stanley R. Szymanski, Livingston, N. Y. (Major, MC, AUS)
 Herman Tarnower, Scarsdale, N. Y. (Lt. Col., MC, AUS)
 Thomas Van Orden Urmy, Boston, Mass. (Lt. Col., MC, AUS)
 Ernest J. Vogel, Arlington, Mass. (Capt., MC, AUS)
 Norton W. Voorhies, New Orleans, La. (Capt., MC, AUS)
 Joseph C. Watts, Bayside, L. I., N. Y. (Major, MC, AUS)
 Edward A. Wilkerson, Houston, Tex. (Lt. Col., MC, AUS)
 Ellis W. Willhelmy, La Jolla, Calif. (Lt. Comdr., MC, USNR)
 Willis D. Wright, Omaha, Nebr. (Comdr., MC, USNR)
 Joseph Ziskind, New Orleans, La. (Major, MC, AUS)

DR. T. GRIER MILLER APPOINTED A. C. P. MARSHAL

Dr. T. Grier Miller, F.A.C.P., Philadelphia, newly elected Regent of the American College of Physicians, has been appointed by the President, Dr. David P. Barr, as official Convocational Marshal of the College, succeeding Dr. Reginald Fitz, F.A.C.P., Boston, who has resigned.

FOURTH INTERNATIONAL CONGRESS ON TROPICAL MEDICINE AND MALARIA TO BE HELD IN THE UNITED STATES

Through the instrumentality of the American Academy of Tropical Medicine plans are under way for the organization of the Fourth International Congress on Tropical Medicine and Malaria to be held in the United States, possibly during 1947, under the official sponsorship of the United States Government, with the collaboration of a number of interested medical and scientific organizations. Already the Southern Medical Association, The American Society of Tropical Medicine, The American Academy of Tropical Medicine, the National Malaria Society, the American College of Physicians and others have adopted resolutions looking toward the organization of such an International Congress and to assist therewith. Dr. Joseph M. Hayman, Jr., F.A.C.P., Professor of Clinical Medicine at Western Reserve University School of Medicine, Cleveland, has been appointed as the official representative of the American College of Physicians in initiating the invitations and making preliminary arrangements.

SPECIAL NOTICE

Announcement is made by Surgeon General Thomas Parran of the U. S. Public Health Service that a grant for the establishment of 125 Fellowships to train physicians and sanitary engineers in public health has just been approved by the National Foundation for Infantile Paralysis.

Each Fellowship provides a year's graduate training in a school of public health or a school of sanitary engineering. The Fellowships will be administered by the Committee on Training of Public Health Personnel, which consists of representatives of schools of public health, the State and Territorial Health Officers, the American Public Health Association and the U. S. Public Health Service.

The Fellowships are available either during the academic year beginning in the fall of 1946 or the fall of 1947, and are open to men and women, citizens of the United States under 45 years of age.

The purpose of the Fellowships is to aid in the recruitment of trained health officers, directors of special medical services, and public health engineers to help fill some of the 900 vacancies in public health medical positions and 300 vacancies for public health engineers, existing in State and local health departments over the country. The Fellowships are reserved for newcomers to the public health field, and are not open to employees in State and local health departments, for whom Federal Grants-in-Aid are already available to the States.

Applicants for Fellowships may secure further details by writing to the Surgeon General, U. S. Public Health Service, Attention: Public Health Training, 19th and Constitution Avenue NW., Washington 25, D. C. Owing to the anticipated heavy enrollment in graduate schools, completed applications for training in the fall term of 1946 should be filed promptly. The awards committee will act on applications on the following dates: June 15, July 1, July 15 and August 1.

OBITUARIES

DR. ROLLIN H. STEVENS

Dr. Rollin H. Stevens died of leukemia, after a prolonged illness, on May 17, 1946. Dr. Stevens was born in 1868 in Blenheim, Ontario. He received his degree in medicine in 1889 from the University of Michigan. Early in his career he became interested in radiology and quickly became a leader in his chosen field. He was one of the first to organize a hospital x-ray department in Michigan, and was the first doctor in the middle west to use radium in the treatment of disease.

To honor his enthusiasm, his loyalty to his profession and his many accomplishments, the Journal of Radiology, on his seventieth birthday, dedicated an entire issue to him. This was known as the Rollin Howard Stevens birthday issue.

Dr. Stevens became Radiologist to Grace Hospital, Detroit, in 1903, and Consulting Radiologist to the Wayne County Hospital in 1933. He was Chairman of the Wayne County Cancer Committee in 1939 to 1940, Trustee of the American Board of Radiology in 1934, and served as Secretary of the Radiological Research Institute. He was a Diplomate of the American Board of Internal Medicine and a Fellow of the American College of Physicians since 1920.

DOUGLAS DONALD, M.D., F.A.C.P.,
Governor for Michigan

DR. ROBERT WILSON

Robert Wilson, Sr., A.B., M.D., LL.D., D.C.L., Dean Emeritus and Professor Emeritus of Medicine, Medical College of the State of South Carolina, Charleston, S. C., died of coronary occlusion and pneumonia on May 20, 1946, after a brief illness.

Dr. Wilson was born on August 23, 1867, at Stateburg, S.C. He attended the College of Charleston and the University of South Carolina (then South Carolina College), where he received the A.B. degree. After receiving the M.D. degree from the Medical College of the State of South Carolina in 1892, he entered private practice in Charleston. He became attached to the teaching staff of the Medical College in 1893 and advanced through the ranks to the professorship of medicine in 1913, at which time he played a major rôle in the transfer of the school to state ownership and operation.

He became dean in 1908, a post which he held until December 1943, when he resigned the deanship and professorship of medicine and became special lecturer in medical history. Along with his medical school positions went membership in the staff of the Roper Hospital of which he was Physician-in-Chief from 1913 to 1943.

Always active in medical organization affairs, Dr. Wilson had served as president of the South Carolina Medical Association and the Southern

Medical Association. He was First Vice-President of the American Medical Association in 1910-11. A Fellow of the American College of Physicians since 1923, he served as a member of the Board of Governors until 1936. He was a diplomate of the American Board of Internal Medicine and was a member of the American Society of Tropical Medicine, the National Association for the Study and Prevention of Tuberculosis, the American Climatological and Clinical Society, as well as the usual local and national medical associations. He also belonged to Sigma Alpha Epsilon, Phi Chi and Phi Beta Kappa fraternities.

Deeply interested in civic matters, he was Chairman of the South Carolina State Board of Health from 1907 to 1935. In 1939 he was awarded the American Legion's distinguished service plaque.

He had received the honorary degree of LL.D. from the College of Charleston and the University of South Carolina and the D.C.L. from the University of the South.

A life more complete in service and accomplishment is seldom recorded among us.

KENNETH M. LYNCH, M.D., F.A.C.P.,
Governor for South Carolina

DR. LOUIS HAMMAN

On April 28, 1946, Baltimore awakened with a shock to learn of the death of Dr. Louis Hamman. Dr. Hamman had long been associated with the College, and his interest in the work of the College in Maryland was always a great help to those in charge.

Dr. Hamman was born December 21, 1877. He obtained his A.B. degree in Rock Hill College, Ellicott City, Maryland, graduated from the Johns Hopkins University School of Medicine in 1901, did postgraduate work in Berlin, returned to the United States and became a house officer in New York Hospital, 1901-1902. For many years Dr. Hamman has been Associate Professor of Clinical Medicine at the Johns Hopkins University School of Medicine and visiting physician at the Johns Hopkins Hospital of Baltimore.

Dr. Hamman was a Fellow of the College and at one time member of the Board of Internal Medicine. He took a prominent part in the Association of the American Physicians. He was a member of the Society for Clinical Investigation and a Fellow of the American Medical Association. He published many papers and wrote the chapter on "Diseases of the Bronchi," Oxford University Press.

To those young men who have graduated from the Johns Hopkins Hospital it will be with a great deal of sorrow that they learn of Dr. Hamman's death. Baltimore and American medicine can ill afford to lose many of this type of man.

WETHERBEE FORT, M.D., F.A.C.P.,
Governor for Maryland

DR. DANIEL L. DOZZI

Dr. Daniel L. Dozzi, a Fellow of The American College of Physicians since 1941, died on May 18, 1946.

He was born on May 11, 1907, at Cardiff, Colorado. He received the A.B. degree from the University of Utah in 1929 and the M.D. degree from the University of Pennsylvania in 1932.

Dr. Dozzi did postgraduate work at the University of Pennsylvania and received the degree of M.M.S. in February 1939, and D.M.S. in June, 1939. From 1935 to 1939 he was a Clinical Assistant at Graduate Hospital. He was Instructor in Medicine in the Graduate School of Medicine at the University of Pennsylvania in 1939. From 1937 to 1939 Dr. Dozzi was Assistant Physician to the Chestnut Hill Hospital and in 1939 was appointed as Associate Physician to that hospital. Since 1939 he was affiliated with the Department of Surgical Research in the University of Pennsylvania.

Dr. Dozzi was a member of the Philadelphia County Medical Society, Medical Society of the State of Pennsylvania and the American Medical Association.

His passing at the peak of a brilliant career with a promising future is a great loss to the medical profession and the community.

EDWARD L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. FREDERIC MOIR HANES

In the untimely death of Dr. Frederic Moir Hanes, Professor of Medicine at Duke University, North Carolina medicine suffered the loss of one of its most distinguished members. Naturally endowed with great talents and resources he used them to the fullest extent. He had an amazing sense of values, and applied the same rigid standards of intellectual honesty, ethics and training to himself as he did to others. He knew and was personally interested in all who worked for him and with him, and the acts of kindness and consideration that he quietly extended over a period of years are almost unnumbered. I can think of few others who in appearance, intellect, training, ability and versatility could compare with him. I had a profound admiration for this truly great and versatile man whose life added so much to his distinguished family, his State, his profession, his students and the institution that he represented.

The following obituary was written for the North Carolina Medical Journal by Dr. David Cayer, of the Bowman Gray School of Medicine, who was one of his students and residents, and published by his life long friend, Dr. Wingate Johnson. Not being able to improve upon it, I submit it for publication in the official organ of the American College of Physicians of which Dr. Hanes was a distinguished member.

PAUL F. WHITAKER, M.D.,
Governor for North Carolina

On March 25, 1946 the medical profession suffered the loss of an outstanding colleague, Dr. Frederic Moir Hanes, F.A.C.P., and the North Carolina Medical Journal lost one of the most valuable members of its editorial board. Rarely does any one combine so well the necessary qualities for competence in medicine listed by Hippocrates: a natural disposition, instruction, a favorable position for the study, early tuition and love of labor.

A simple enumeration of the honors which came to Fred Hanes in his lifetime would alone testify to the position of esteem which he held among his associates. His scholastic achievements were recognized early by his election to Phi Beta Kappa. While a medical student at Johns Hopkins, he described the rare condition of familial telangiectasia with such clarity and conciseness that no one has improved upon his original work. Dr. Thayer, renowned professor of medicine at Johns Hopkins, spoke of Dr. Hanes as the most brilliant student to come out of Hopkins.

During the period from his graduation until the beginning of World War I, Dr. Hanes delved into many fields of medicine, both in this country and abroad, and laid the foundation of his unusually broad knowledge of the subject. He was for a while associated with the Rockefeller Institute, where he investigated fat metabolism and digestion, the motility of cancer cells, and bacteriologic problems, developing and utilizing technic of tissue and check embryo culture which today are among the most valuable methods in such research. When the World War began, he left the position which he then held as professor of therapeutics at the Medical College of Virginia to become commander of Base Hospital No. 65, which served with such distinction in France from 1917 to 1919. At the end of the war he returned to his native city of Winston-Salem to practice internal medicine.

In 1933 Dr. Hanes was asked to head the Department of Medicine at the Duke University School of Medicine. Although few men of his age would have attempted to return to academic medicine, and even fewer would have been able to do so, his adaptability, versatility, and remarkable ability to stay abreast of medical progress were more than adequate for the task. He fostered research projects and participated in them, contributed scientific articles to leading journals, and was the author of sections on sprue and fungus diseases in well known systems of medicine.

He did not, however, consider these endeavors as his most valuable contribution to medicine. When on occasion he was praised for his accomplishments, he was wont to point to his house staff and students and say, "These, I hope, will be my greatest contributions." He was proud of the young men whom he helped to train, and took a truly paternal interest in them. He demanded of them the same high standards of integrity and efficiency that he did of himself. Often, rather than allow a promising house officer with inadequate experience to begin the practice of medicine, he would provide sufficient funds to enable him to continue his hospital training. Most of his many kind and generous deeds were done so quietly that they will remain unknown. Many persons in need of medical and surgical atten-

tion came to the hospital bearing a note signed in his distinctive hand: "Please admit to the hospital and send bill to me."

Dr. Hanes was an outstanding example of intellectual honesty and was intolerant only of sham or pretense. In spite of a full devotion to his profession, he possessed a versatility which characterizes truly great men. He was a lover of art, a bibliophile, and an authority on Samuel Johnson. His interest in horticulture is reflected in the beauty of the Sarah Duke gardens, and in the fragrant plants which graced his offices.

Dr. Fred Hanes exemplified the highest type of clinician, teacher, and friend. His dynamic personality, his intellectual honesty, his keen and discriminating mind, and his devotion to the best in medical education all combine to make a splendid heritage for North Carolina medicine.

DAVID CAYER, M.D.

DR. CHARLES SAMUEL KIBLER

With the death of Charles Samuel Kibler, M.D., S.B., F.A.C.P., Arizona has indeed lost one of its first citizens and medical leaders for about 25 years. Dr. Kibler was born in Newark, Ohio on July 25, 1889. He did his pre-medical work and first year of medicine in the Ohio State University, completing his medical work and receiving his degree at Rush Medical College in 1914. Following his two years of internship at Cook County Hospital and a year of residency in the Presbyterian Hospital in Chicago, Dr. Kibler entered the medical service of the army, being discharged in 1919 as a Captain. He was Assistant Medical Chief of the Base Hospital at Camp Shelby, Mississippi while in the service.

He came to Tucson where he engaged in the active practice of medicine and continued there until his death. He practised his specialty of internal medicine, being a diplomate of the American Board of Internal Medicine. He held many offices in the Medical Societies. He was a former President of the Pima County Medical Society, former Governor for Arizona of the American College of Chest Physicians, Arizona representative on the Board of Directors of the National Tuberculosis Association, member of the American Trudeau Society, and American Association for the Study of Allergy, and Fellow of the American College of Physicians since 1926.

Dr. Kibler published numerous papers dealing with tuberculosis, allergy, and kindred subjects. Dr. Kibler was very active in the practice of medicine right up to the day of his death which was by coronary occlusion.

His wisdom and medical acumen have ever been an inspiration to his colleagues. He will be deeply missed.

FRED G. HOLMES, M.D., F.A.C.P.
Governor for Arizona

DR. ALEXANDER BERKELEY MOORE

Dr. Alexander B. Moore, F.A.C.P., one of the most widely known radiologists of America, died in Emergency Hospital, Washington, D. C., on March 8, 1946.

Dr. Moore was born in Aldie, Virginia, in 1883. He obtained his medical degree at the University of Virginia in 1907, practiced for a year at The Plains, Virginia, and for a short time in a medical clinic in Seattle, Washington. In 1909, he entered the radiological department of the Mayo Clinic with which he was identified for more than twenty years. He was a Captain in the Medical Corps of the United States Army during the First World War and at the close of the war was Chief Radiological Consultant of the Second Army, A.E.F., with headquarters at Toul, France. He returned to the Mayo Clinic in 1919 and in 1926 became head of the radiological department. In 1930 he became associated with Drs. Groover, Christie and Merritt in Washington, D. C., and for the remainder of his life was head of the radiological department of the Emergency Hospital in that city.

Dr. Moore was a Fellow of the American College of Physicians, Fellow of the American Medical Association, Member of the Medical Society of the District of Columbia, Member of the American Roentgen Ray Society and Member of the Radiological Society of North America.

"Sandy" Moore will long be remembered by his medical colleagues as a radiological diagnostician of unusual ability, especially in diseases of the chest and gastrointestinal tract. The loss of a good comrade and kindly human companion for whom they had a deep abiding affection will be felt by friends throughout the nation.

ARTHUR C. CHRISTIE, M.D., F.A.C.P.

DR. WALLER S. LEATHERS

Dr. Waller S. Leathers, F.A.C.P., died in Nashville, Tennessee, January 26, 1946. He was born in Virginia in 1874. He graduated in Medicine from the University of Virginia in 1895 and took postgraduate work at Johns Hopkins, The University of Chicago and Harvard Medical School.

After serving as Professor of Chemistry at the Miller School of Virginia 1896-1897 Dr. Leathers became Professor of Biology at the University of South Carolina. In 1899 he accepted the chair of Zoology at the University of Mississippi and later was made head of the Department of Physiology and Hygiene. His work became so outstanding that he was then made Dean of the Medical Department.

From 1910-1924 Dr. Leathers served as Director of Public Health in the State of Mississippi. It was during this period that Mississippi made its greatest advances in public health.

In 1924 he was called to the faculty of Vanderbilt University School of Medicine, becoming its Dean in 1928.

In 1918 he was president of the Mississippi State Medical Association.

In 1922 he became president of the Southern Medical Association. It was in 1923 that he was made a Fellow in the American College of Physicians. He was President of the Tennessee Academy of Science in 1926; vice-president of the American Association for the Advancement of Science in 1928; President of the American Public Health Association in 1940 and President of the Association of American Medical Colleges in 1943.

Under the skilled leadership of Dr. Leathers the Vanderbilt Medical School became one of the outstanding medical schools of the country. His great interest in preventive medicine and public health and his untiring work in those problems pertaining to sanitation and health were responsible for great improvement in living conditions in the entire South.

The many honors that came to Dr. Leathers were in recognition of his leadership in public health, in medical science and in better medical education.

WILLIAM C. CHANEY, M.D., F.A.C.P.,
Governor for Tennessee

DR. EUGENE ROSAMOND

Dr. Eugene Rosamond, F.A.C.P., died in Memphis, Tennessee, Dec. 12, 1945. He was accidentally shot in the cervical region of his spine in 1940, resulting in paralysis in all four extremities.

Dr. Rosamond was born at Cedar Chapel in 1880. He received the degree of A.B. at Ouachita College, Arkansas, in 1899, and then studied Medicine at the University of Louisville, Kentucky, where he graduated in 1905. In preparation for specializing in Pediatrics Dr. Rosamond did post-graduate work at the New York Polyclinic Hospital and New York Post-graduate Hospital.

He was a member of the Central States Pediatric Society, The Memphis and Shelby County Medical Society and the American Medical Association. He became a Fellow of the American College of Physicians in 1929.

For many years Dr. Rosamond had been one of the leading Pediatricians in the South. His comprehensive knowledge of his specialty together with an ability to talk well were responsible for his appearing frequently upon medical programs all over the country.

WILLIAM C. CHANEY, M.D., F.A.C.P.,
Governor for Tennessee

DR. DONALD BLAIR LOWE

Donald Blair Lowe, A.B., M.D., F.A.C.P., died in Akron, Ohio, March 2, 1946, of acute hemorrhagic pancreatitis.

Dr. Lowe was born August 1, 1883, at Kingsville, Ohio. He attended Western Reserve University in Cleveland where he received his A.B. degree in 1909 and his M.D. degree in 1912. The following two years he served as instructor in medicine at that University. In 1915 he was appointed Director of the Medical Department of B. F. Goodrich, Akron, Ohio, which position he held during his whole life. Under his direction this Medical

Department assumed greater and greater importance and Dr. Lowe was among the foremost of the industrial physicians in this County.

He served as President of the American Association of Industrial Physicians in 1932 to 1933. His keenness of thought prompted him to suggest many industrial research problems to other investigators.

He was admitted to the Summit County Medical Society February 1, 1916, and became its President in 1939 after serving faithfully on many of its standing committees.

For many years he was a member of the staff in Internal Medicine of The City Hospital of Akron and served as Hospital Chief of Staff in 1936. He was a Fellow of the American College of Physicians and a member of Delta Upsilon Fraternity.

Dr. Lowe was one of the most highly respected physicians of this State. His activities ranged from an intense desire to teach younger doctors to participation in all matters of civic interest. He was steadfast in his opposition to sham and pretense and demanded of his associates and colleagues the same intensity of purpose which he had.

Since his death there has been set up a fund to be known as The Donald Blair Lowe Fund for educational purposes.

ALEXANDER PIERCE ORMOND, M.D., F.A.C.P.

DR. CLARENCE L. HYDE

In the death of Dr. Clarence L. Hyde, F.A.C.P., on December 1, 1945, the medical profession lost a distinguished leader known both nationally and internationally for his work in the prevention, control, and treatment of tuberculosis.

Dr. Hyde was born May 23, 1878, the son of the Reverend Melancthon Cleveland Hyde, then Rector of All Saints Episcopal Church, Buffalo, New York, and Elizabeth Ludlam (Stoutenburgh) Hyde.

He received his medical training at the University of Michigan, from which he was graduated in 1906, and later served as house officer at the Homeopathic Hospital of Montreal, Canada. In 1909, he married Baca Luz Chisholm of Montreal, who survives him, together with their two children, Cleveland Chisholm Hyde and Elizabeth Margaret Hyde.

From 1909 to 1911, Dr. Hyde served as Director of the Division of Tuberculosis in the Dept. of Health of Buffalo, New York. During his residence in Buffalo, he was also Consultant in Tuberculosis at the Ernest Wende Hospital and at Buffalo City Hospital. His unusual ability was quickly appreciated and he was called to be Superintendent of the J. M. Adam Memorial Hospital, Perrysburg, New York, where his work from 1913 to 1920 received national attention. In the latter year, Dr. Hyde became Superintendent of the Edwin Shaw Sanatorium, Akron, Ohio, where he remained until the time of his death.

Dr. Hyde was one of the initiators of the county-wide plan for the control of tuberculosis. Soon after taking up his duties in Akron and Summit

County, he established the Municipal Tuberculosis Clinic with subsidiary clinics in the smaller communities where from the very beginning a chest roentgenogram was a part of every examination. He was an early advocate of the use of collapse therapy measures and at the same time stressed the value of absolute and prolonged bed rest. He was recognized widely as a pioneer in the use of heliotherapy in America for the treatment of extrapulmonary forms of tuberculosis. He attacked the problem of tuberculosis control by means of continuous and effective education of the public, a meticulous case-finding program, and a modern and attractive tuberculosis hospital where treatment and rehabilitation of the patient were carried out scientifically and sympathetically.

The soundness of Dr. Hyde's ideas is amply attested by the results of his labors. The electorate of Akron and Summit County has repeatedly approved tax levies to support the Sanatorium by majorities as great as 85 per cent; the per capita seal sale has increased each year to become the highest of all the metropolitan counties in Ohio; the percentage of cases of tuberculosis diagnosed in the incipient stage of the disease has risen steadily; finally, the tuberculosis death rate in Akron has decreased until it is one of the lowest, if not the lowest, among the 42 large cities of the nation.

Dr. Hyde was a fellow of the American College of Physicians, the American Medical Association, the National Tuberculosis Association, and the American Trudeau Society. He served as President of the Summit County Medical Society in 1928. In 1934, he was an official delegate representing the United States to the Ninth Conference of the International Union Against Tuberculosis held in Warsaw, Poland, where he discussed "Treatment of Tuberculosis of the Bones and Joints."

Dr. Hyde will be remembered not only for his distinguished medical career but also for the imprint of his life and character upon an amazingly wide circle of friends. A genial, kindly man with an extraordinary capacity for friendship, Dr. Hyde radiated confidence. He helped many through critical times by the faith he inspired in them. All through his life, his active leadership in the church reflected his early training in a clergyman's home. He was the embodiment of Christian kindness and courtesy and one of the most beloved men in the communities he served so well.

The Rector of St. Paul's Parish, Akron, in which Dr. Hyde served as Vestryman for over twenty years, says of him:

"He was easily the St. John of our Vestry, indeed the most spiritually minded man I have ever known. His goodness was never heavy. People in all walks of life loved to be near him, and found themselves enriched by his friendship. He was eternally young in spirit. His hearty laugh was like a tonic. As I think of him I recall a line of poetry which at the moment I cannot identify—'No beggar ever felt him condescend, nor prince presume.' He was humble, as all great men are, and like the Master he served so well, 'went about doing good.' May light perpetual shine upon him!"

THEODORE L. BLISS, M.D., F.A.C.P.,

Akron, Ohio

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THE PROBLEM OF PROLONGED HEPATITIS WITH PARTICULAR REFERENCE TO THE CHOLANGI- OLITIC TYPE AND TO THE DEVELOPMENT OF CHOLANGIOLITIC CIRRHOSIS OF THE LIVER *

By CECIL JAMES WATSON, M.D., Ph.D., F.A.C.P., and FREDERICK
WILLIAM HOFFBAUER, M.S., M.D., *Minneapolis, Minnesota*

BOTH sporadic and epidemic jaundice have been generally referred to for many years as "catarrhal" in character. It is well known that this term stems from the early concept of Bamberger¹ and Virchow² of a catarrhal or mucous inflammation of the papilla of Vater, a concept which appears to have been an elaboration, on the grounds of anatomic studies, of the so-called "gastroduodenal catarrh and jaundice" of the earlier Irish clinicians, notably Stokes³ and Graves.⁴ The earlier literature has been adequately reviewed by Eppinger⁵ and Lichtman.⁶ Attention may be called again to the clear statement of Flindt⁷ in 1890, that so-called catarrhal jaundice is, in the main, a diffuse parenchymatous liver disease rather than a catarrh of the ampulla. A number of years later, during World War I, Eppinger⁸ studied the livers of four soldiers killed in action, who were suffering from "catarrhal" jaundice at the time of death. In each instance the papilla of Vater and the bile ducts appeared normal, but the liver exhibited the histologic picture of an "acute destructive hepatitis." Entirely similar findings and conclusions were reported by Lindstedt,⁹ later by Klemperer, Killian and Heyd,¹⁰ and by Gaskell.¹¹ Recent studies^{12, 13} of liver histology, as afforded by aspiration liver biopsy, have quite uniformly confirmed these earlier reports so that it may now be accepted that what has hitherto been designated as catarrhal

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jaundice is hepatitis, with but rare exception. Eppinger⁵ emphasizes the great rarity of true catarrhal jaundice or papillitis by pointing out that but three cases have ever been proved at necropsy.

Past wars have had their epidemics of jaundice, the "jaundice of the camps," or "of the campaign." The disease was common in the American Civil War, in the Crimean War, and in the Balkan campaigns of World War I. In the present war epidemic hepatitis has been a medical problem of the first order of magnitude, often "second in importance only to malaria and venereal disease."¹⁴ This is scarcely surprising when one considers the important factors contributed by three of the four horsemen, i.e. (1) war; the crowding, poor sanitation and fatigue incident to it, (2) famine; the deleterious effect of malnutrition on the liver, and (3) pestilence; the reduction of the resistance of the liver incident to other infections, notably those of the *Salmonella* and *Shigella* groups. The frequent association of hepatitis with the latter group of diseases is well known.

Unfortunately enough, the incidence of hepatitis in World War II has been considerably increased in the attempt to limit or prevent other diseases. The transmission of icterogenic agents to healthy individuals has occurred through the administration of pooled serum or plasma, or products containing one or the other, as for example yellow fever vaccine as formerly used.^{15, 16, 17} This type of hepatitis has come to be known as "homologous serum jaundice," regardless of whether the source was yellow fever vaccine, measles or mumps convalescent serum, or whole blood or plasma transfusions. The subject of homologous serum jaundice has been thoroughly considered in several recent papers.^{15, 18, 19, 20, 21} The incubation period of this type of hepatitis, usually in the neighborhood of 60 to 120 days, is usually more than twice as long as that of the spontaneous form.^{21c} This difference has been regarded by many as indicating a different etiology, but it is entirely possible, as suggested by Neefe and his co-workers,^{21a} that the length of incubation period is determined by the portal of entry. This is also indicated by the studies of Havens and his co-workers.^{22a} Furthermore, the study of Neefe and his associates²¹ revealed clearly that hepatic involvement following injection of icterogenic serum, is commonly present long before the appearance of jaundice, if carefully sought by means of suitable laboratory tests. Recent studies by Neefe and co-workers^{21b, c} indicate strongly that the diseases are at least immunologically distinct. Siede and Luz²³ have reported serial passage of the virus of the epidemic type in chick embryos and interestingly enough, the livers were found to be most susceptible. These results have not been confirmed.

Witts¹⁴ has postulated a fundamental difference between homologous serum jaundice and the spontaneous epidemic variety on the basis of an increased susceptibility to the latter in individuals having had the former. One might take the opposite viewpoint, however, that an immunity is not conferred, and that the liver is simply rendered more susceptible by the first

attack. Multiple attacks of sporadic or so-called "catarrhal" jaundice, in the same individual, are very well known, and have also been observed in the epidemic form.²³ Oliphant's studies²⁴ were of much interest to this whole question. These observations, although limited to a small series of volunteers, indicated that an attack of homologous serum jaundice 12 to 18 months previously, appeared to confer an immunity against subsequent infection whether of the spontaneous variety, or that due to yellow fever vaccine containing human serum. As indicated above, however, the more recent studies of Neefe and his associates,^{21c} and of Havens^{22b} failed to reveal cross immunity.

Regardless of whether the icterogenic agent gains access by parenteral administration, as in homologous serum jaundice, or by droplet infection or ingestion, as seems probable for spontaneous epidemic jaundice, the resulting hepatitis produces a relatively long disability, the average duration of jaundice in a recent epidemic being approximately 27 days.²⁵ In most instances a considerable further period of weakness and easy fatigability prevents early resumption of rigorous activity.

The question of the duration of jaundice is of considerable interest with respect to the anatomic type of hepatitis. It will be remembered that Eppinger² described two clinical and anatomic (histologic) varieties of hepatitis: (1) the hepatocellular form, (2) the periacinar or cholangitic form. The first of these is generally regarded as the common type, whether sporadic or epidemic. This form, according to Eppinger, is characterized by jaundice of relatively short duration, usually from two to four weeks, with considerable evidence of deranged liver cell function. The second variety is characterized by a more severe jaundice, of much longer duration, commonly two to four months. The liver and spleen are usually enlarged, the stools are acholic and urobilinogen is commonly absent from the urine, at least for long periods. This type obviously offers the greatest difficulty in differential diagnosis, and as Eppinger has pointed out it is a condition in which an operation, carried out with the intention of relieving an extrahepatic biliary obstruction, is likely to be both disappointing and hazardous. The present study has been concerned particularly with cases of this type, which will be referred to henceforth as *cholangiolitic hepatitis*. The reasons for the use of this term are discussed subsequently. A number of illustrative examples are described in the following:

CASE REPORTS

Case 1. D. G., male, aged 18. This patient suffered a brief attack of diarrhea early in December, 1942, shortly followed by an episode of painless jaundice that lasted until June, 1943. At the time of onset he was living with a brother who had had jaundice in August, 1942. The patient was inducted into the Navy in July, 1943, and received yellow fever vaccine during his preliminary training period. He felt well until Nov. 5, 1943, when he had a brief attack of diarrhea; jaundice appeared within a few days. It may be noted, however, that he had observed dark urine since

about October 15. He stated that he had recently heard from his brother, then in the Army, and that he too was ill with a recurrent attack of jaundice. This was subsequently confirmed in a letter from an Army Medical Officer. The patient was admitted to the Medical Service on November 20. He was well developed and well nourished, apparently comfortable but quiet and mildly apathetic. The liver was found to be 5 cm. below the rib margin in the right mid-clavicular line; it was smooth and not tender. The spleen was palpable at times and again it could not be felt.

The patient remained in the hospital until February 7, 1944. Treatment included a high carbohydrate (350 gm.), high protein (150 gm.; 50 per cent meat), low fat (50 gm.), "liver" diet with supplementary vitamin B complex and vitamin C. Decholin* (3 c.c. of a 20 per cent solution) was given twice daily intravenously from December 5 to January 6 inclusive. It was doubtful that this had any effect since bile did not begin to return to the bowel until December 21, a full two weeks after commencement of this therapy. This is seen in the relationships of the serum bilirubin, urine and feces urobilinogen as shown in figure 1. A composite liver function study,²⁶ carried

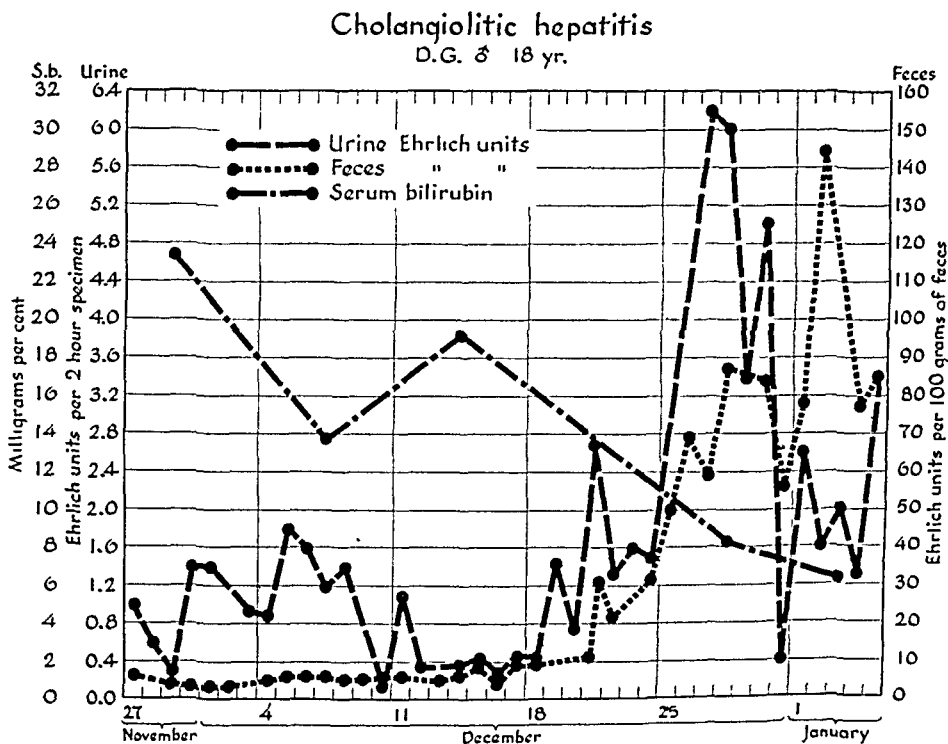


FIG. 1. (Case 1) Serial data for serum bilirubin, urine and feces Ehrlich units as obtained in this case of cholangiolitic hepatitis. Evidence of high grade or complete exclusion of bile from the intestine is noted during the first half of the period shown. The relative increase of Ehrlich units in the urine from November 30 to December 11 was interpreted as indicative of hepatic parenchymal damage, which is shown more strikingly during the opening phase from December 18 onward. (Reproduced from the article by Dr. C. J. Watson²⁷ in the *American Journal of Clinical Pathology*, 1944, xiv, 613; courtesy of Williams and Wilkins Co., Baltimore.)

out between December 8 and 13, revealed a pattern characteristic of a regurgitation jaundice with complete biliary obstruction but with relatively normal liver cell function (see figure 2). The negative cephalin cholesterol flocculation is especially noteworthy.

* Riedel-deHaen, Inc.

23. The leukocyte count ranged from 9950 to 13,200 with from 66 to 80 per cent neutrophils. On admission the count was 13,200 with 66 per cent neutrophils.

A needle biopsy of the liver was done on November 29. The technic employed has been described elsewhere.²⁶ The sections revealed a surprisingly normal histology in spite of the marked jaundice at this time (Plate I, a). Some bilirubin staining of the central lobular cells with occasional bile thrombi was apparent. The periportal cellular infiltration was not marked.

After December 21, it became evident that bile was returning to the intestine as determined by the quantitative feces Ehrlich reaction.²⁷ There was progressive improvement thereafter. By February 7 the patient felt very well; there was but slight residual icterus, and he was discharged from the medical service.

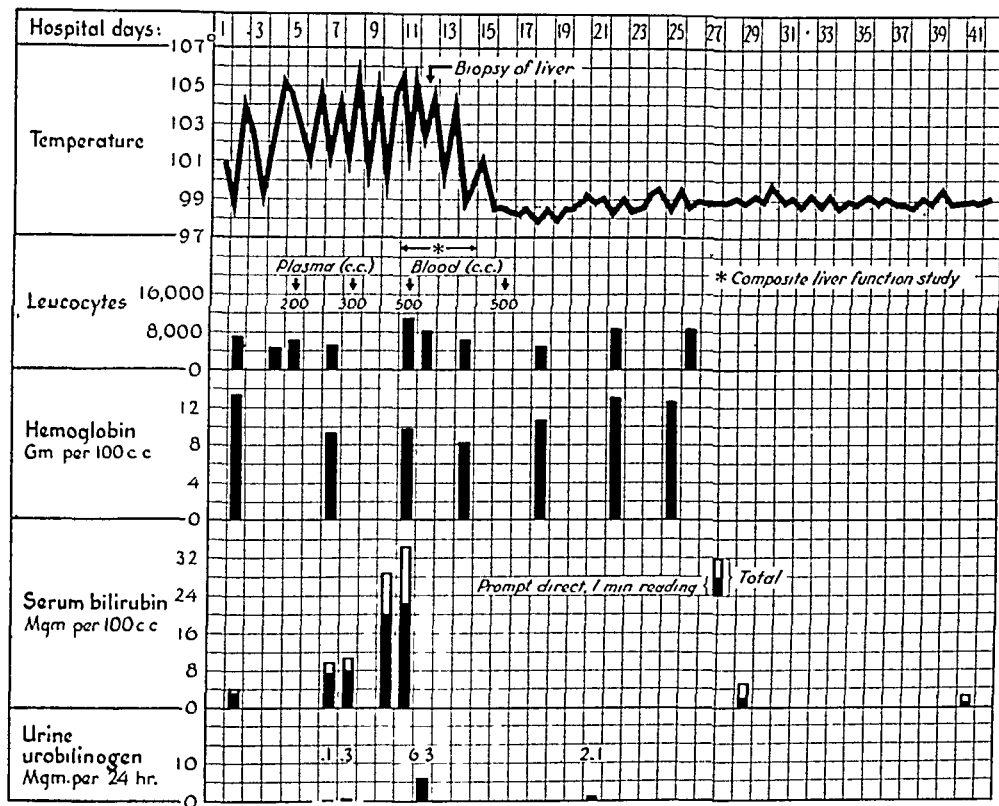


FIG. 3. (Case 2) Clinical course of cholangiolitic hepatitis in a 15 year old girl.

Case 2. D. K., female, aged 15. This patient was first admitted on the Pediatric Service* of the University Hospital on July 20, 1943. At this time a right indirect inguinal hernia was repaired. A wound infection occurred and the wound opened and drained; culture of the pus yielded hemolytic streptococci. After further bed rest and sulfonamide therapy the wound healed and the patient was discharged on August 20, 1943. She was readmitted on the Pediatric Service on October 1, 1943, complaining of headache and malaise, nausea, vomiting and fever of about five days' duration. On the day before admission she suffered a chill and the temperature rose to 104° F. Chills and marked fever characterized the hospital course for the first 14 days. The temperature elevation was characterized by daily rises to from 104° to 106° F., the peak usually being reached in the evening, the temperature then falling to nor-

* We are indebted to Dr. Irvine McQuarrie for permission to study this patient and report the findings.

mal or nearly normal levels in the morning (see figure 3).. Slight icterus was first noted at the time of admission and it was subsequently determined that early in September, 1943, the patient had stayed in the same house with three children who had mild jaundice. The serum bilirubin on the day following admission was: 1', 3.4 mg.; total 4.0 mg. The 1' bilirubin is synonymous with the prompt reacting type, elevation of which is believed to characterize regurgitation as contrasted with retention jaundice. The difference between the total and the 1' represents the delayed or indirect reacting fraction.²⁸ The jaundice rapidly deepened and six days later the values were: 1', 7.98 mg.; total, 10.5 mg. The physical examination at the time of admission revealed nothing of significance other than mild icterus and some lethargy. The liver and

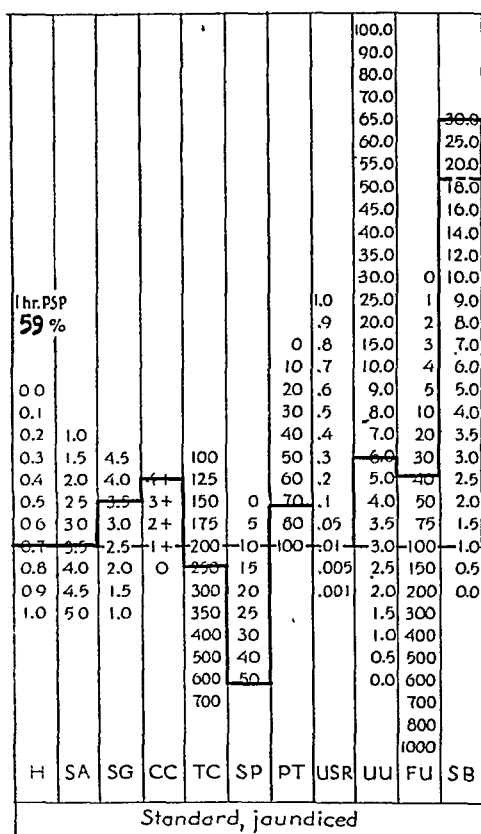


FIG. 4. (Case 2) Liver function studies carried out during febrile period indicated in figure 3, October 11 to 14, 1943.

spleen were not palpable. By the fifth day the liver had become palpable 2 cm. below the costal margin; it was not tender, but there was slight tenderness over the herniorrhaphy scar in the right lower quadrant. Duodenal drainage on this date failed to reveal bilirubin and cholesterol crystals were not observed. A moderate number of pus cells was present. At this time the patient developed a diffuse morbilliform, partly urticarial and itching rash which persisted for several days. Various laboratory findings, as related to the fever and other factors, are shown in figure 3. A composite liver function study was carried out during the period indicated. The data obtained are shown in figure 4. It is seen that there is some evidence of liver functional disturbance, including a positive cephalin cholesterol flocculation. The relative lack of urobilinogenuria was rather surprising with so much fever and the evident presence of an appreciable amount of bile in the intestine.

A liver biopsy was carried out with the Silverman needle. Culture and animal inoculation of a portion of the material obtained was negative. The histologic structure is shown in Plate 1, b. Bilirubin staining of the centers of the lobules was noted, together with a moderate number of bile thrombi. Some increase of leukocytes was seen about the portal spaces, although this was not prominent. No necrosis was observed. The pathologist, Dr. J. S. McCartney, concluded that this was either "obstructive or acute catarrhal jaundice."

The temperature had returned to normal by the fifteenth hospital day. It is of some interest that a transfusion of 500 c.c. of whole blood had been given on the eleventh hospital day, on which the temperature twice reached 106° F., once before and once after the transfusion. On the twelfth day an elevation to 105° was noted, on the thirteenth and fourteenth to 102° and 101°, respectively, after which there was no further fever. The patient had been offered the aforementioned "liver" diet, but during the severe fever had eaten but relatively little. However, she received a liter of 10 per cent glucose in distilled water and the same amount in normal saline, given intravenously, each day until her appetite had improved. On the fifteenth hospital day, at the time the temperature returned to normal, the liver was recorded as three fingers' breadth below the costal margin. From this time forth the patient improved rapidly. On the twenty-ninth day the serum bilirubin had declined to: 1', 2.4 mg.; total, 5.3 mg. On the forty-first day jaundice was no longer manifest, although the serum bilirubin was still elevated: 1', 1.1 mg.; total, 2.6 mg. The patient was discharged feeling entirely well on the forty-second hospital day. She was seen again in the out-patient clinic in March, 1944, five months after discharge. At this time she felt quite well, there was no jaundice and the liver and spleen were not palpable. The serum bilirubin was: 1', 0.2 mg.; total, 0.6 mg. The Hanger cephalin cholesterol flocculation test was recorded as 1 + in 24 hours, 2 + in 48 hours.

Case 3. R. A., male, aged 9. This patient was admitted to the Pediatrics Service of the University Hospital on November 25, 1943.* The mother stated that his illness had commenced during the first week of September, 1943. At this time he had complained of fatigue, malaise and anorexia. He was able to attend school for one week with these symptoms but was so tired that he went to bed as soon as he arrived home each afternoon. A week after the onset of symptoms he developed a moderate diarrhea with occasional vomiting, and it was now observed that the skin was becoming yellow, the urine dark and the stools light. He was seen by the local physician who prescribed certain medicines of undetermined nature, probably a laxative and some form of iron pills. The patient gradually improved and two weeks later was able to return to school, jaundice apparently having disappeared. After he had been in school one week, during which he continued to complain of fatigue and malaise, the jaundice recurred. His condition became worse and he was taken to a private hospital. Shortly thereafter he became irrational and he remained in this state, with occasional lucid intervals, until his admission to the University Hospital three weeks later. On a number of occasions he was violent and difficult to restrain. There were no convulsions. In spite of frequent administration of glucose and saline intravenously, his condition gradually grew worse. During this period there was moderate fever, on but one occasion, however, above 100° F.; this was on November 20 when it rose to 103.8° F. The laboratory record at the private hospital revealed a leukocyte count of 7600 with 77 per cent neutrophils; the urine at the outset contained 4 + urobilinogen but subsequently gave negative tests. The feces were reported as acholic.

It is worthy of note that a neighbor of the patient's had been jaundiced about one month prior to onset of the patient's symptoms. Two months after the patient's

*We are indebted to Dr. Irvine McQuarrie for permission to study this patient and report these findings.

jaundice was first observed, a little girl in the neighborhood had a similar but much milder attack of jaundice.

On admission to the University Hospital the temperature was 100° F., pulse 120, respirations 26, blood pressure 124 mm. Hg systolic and 100 mm. diastolic. The patient appeared chronically ill, markedly malnourished and in a grave condition. He was conscious but could not talk, responding only by movements of the head. An intense icterus of a golden brown hue was present. A few petechiae and ecchymoses were noted. There was increased tonicity of all extremities with a gross regular tremor of the muscles of the upper extremities, and a fine tremor of the hands. A fetor was observed at this time but no note was made as to whether it was the fetor hepaticus or not. Later on this characteristic fetor was present and outspoken. The abdomen was markedly distended; the superficial veins were prominent. There was bulging in the flanks with shifting dullness and a distinct fluid wave. Because of the marked ascites it was impossible to determine whether the liver or spleen was enlarged. Mild edema of the scrotum and legs was noted. The routine urinalysis on admission revealed only a large amount of bilirubin, no urobilinogen (qualitative Ehrlich test only). The hemoglobin was 12.3 gm. per 100 c.c., leukocytes 10,150 with 71 per cent neutrophils from 45 to 82 per cent. Unfortunately, the liver function studies in this case were spread out over a long period of time so that it is impossible to depict the composite liver functional status at one time. Nevertheless, a considerable amount of information was gained. During the first several weeks urobilinogen was tested for in the urine and feces only in qualitative fashion. On November 30 the feces urobilinogen was recorded as 1+. Until December 2 the urine Ehrlich reaction for urobilinogen was consistently negative but from the third on it was usually positive. During the period of December 13 to 17 the feces urobilinogen was determined to be 47.8 mg. per day. The serum bilirubin values during the hospital course were as follows:

Date	Serum bilirubin in mg. per 100 c.c.	
	1'	Total
11-25-43	20.3	33.8
12-13-43	27.6	35.9
12-28-43	13.6	23.9
1-3-44	7.4	16.4
1-11-44	6.2	12.5
1-31-44	2.7	5.6
3-15-44	0.5	1.0

On January 31 the 2-4 p.m. urine sample contained 4.4 Ehrlich units* and on February 3, 4.8 Ehrlich units. As already noted the qualitative test for urobilinogen was quite consistently positive both before and after these dates, except for the first week after admission.

The total proteins of the serum were determined repeatedly, but unfortunately, a fractional study was not carried out at any time. The values for total serum protein in gm. per 100 c.c. on different dates were as follows: 11-25-43, 5.7; 12-8-43, 5.4; 12-28-43, 5.3; 1-11-44, 7.6; 1-31-44, 8.7; 3-15-44, 8.0. In relation to these values it may be noted that there was no recurrence of ascites or edema after January 10. It is quite evident that a striking improvement in protein formation occurred between 12-28-43 and 1-11-44. The cephalin cholesterol flocculation in 24 hours was recorded as follows for the dates given: 12-14-43, 4+; 1-14-44, 4+; 2-11-44, 4+; 9-11-44, 2+. It may be noted that with improvement the sedimentation velocity in-

* Normal upper limit: 1 unit.²⁷

creased, from 15 mm. in 60 minutes on 11-27-43 to 113 mm. on 2-14-44; it was still 50 mm. on 6-15-44, although the jaundice and ascites at this time had long since disappeared. The prothrombin time and response to vitamin K were markedly abnormal. The values are given in the following:

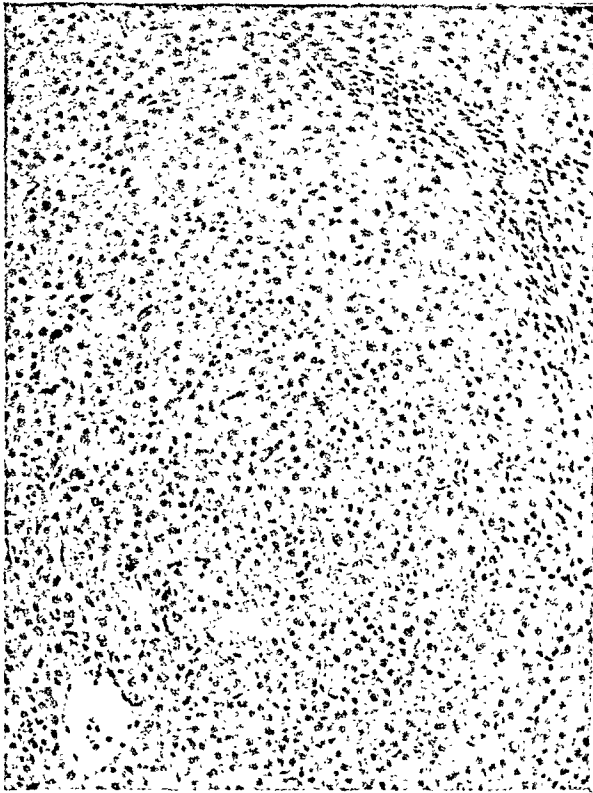
11-27-43	28.4"	(control 16.7")
11-30-43	35.2"	(" 19.6")
12-3-43	29.9"	(" 18.5")
12-7-43	22.4"	(" 16.1")
12-13-43	20.3"	(" 17.1")
1-5-44	32.8"	(" 19.9")
1-11-44	25.2"	(" 18.4")
1-28-44	16.1"	(" 15.5")
3-15-44	22.0"	(" 21.6")
6-10-44	13.2"	(" 11.6")

. With relation to the above data it may be noted that vitamin K* was given intramuscularly each day from admission through January 3, 1944. During the same period the patient received almost daily infusions of human plasma ranging in amount from 150 to 300 c.c. (usually 150 to 200). From December 11 to 20 there was an otitis media which caused daily elevations of temperature to 103 to 104° F. This infection subsided spontaneously. The patient was released from the hospital on January 14, much improved, although not ready for discharge; the release was necessitated by a labor strike against the hospital. He was readmitted on January 29 for further study. At this time the ascites had entirely disappeared. The liver edge was palpable about 6 cm. below the costal margin on the right, and the spleen was easily palpable. On February 8, 1943, a liver biopsy was performed with the Silverman needle. The histologic structure is seen in Plate 1, c. The report of the pathologist, Dr. J. S. McCartney, was as follows: "There is a distinct increase in the portal connective tissue but little if any increase in the number of bile ducts. In the portal tissues there is a mild degree of lymphocytic infiltration. There are fairly numerous dilated bile capillaries and bile thrombi. Most of these are central. A rather large number of liver cells are multinucleated. There are no signs of necrosis or fatty metamorphosis."

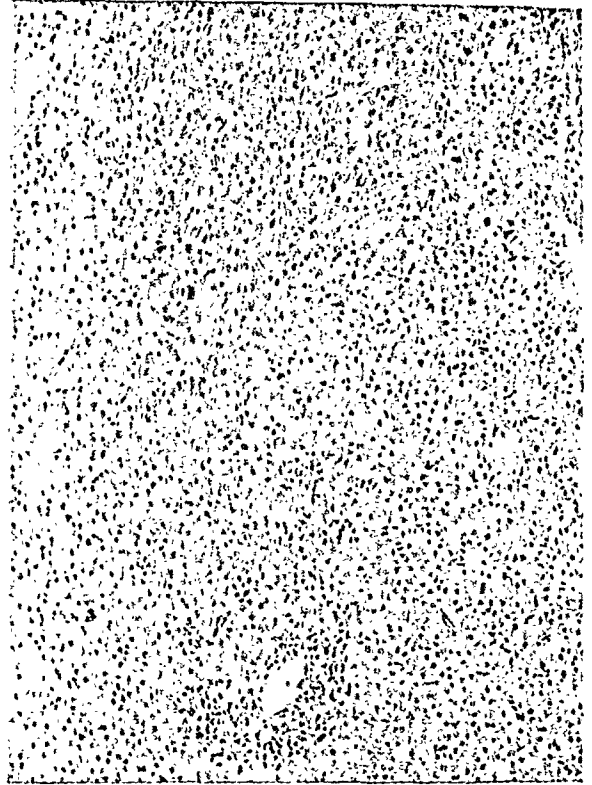
At the time of discharge on February 17, 1944, the patient had a good appetite and was gaining weight. Jaundice was no longer manifest. On March 17 the total serum bilirubin was at the upper limit of normal, but it is noteworthy that the 1' (prompt) bilirubin was still considerably elevated (0.5 mg. per cent). Recent studies⁶³ have shown that the upper limit of normal for the 1' bilirubin probably but rarely exceeds 0.2 mg. per 100 c.c. The liver and spleen were still palpable on August 12, 1944. When he was last seen in the out-patient clinic on Sept. 11, 1944, the cephalin cholesterol flocculation was 2+ in 24 hours, 3+ in 48 hours, and the 2-4 p.m. urine sample contained 1.3 Ehrlich units (upper limit of normal 1.0 unit).

Case 4. V. E., male, aged 29. This patient was admitted to the Medical Service of the University of Minnesota Hospital on October 11, 1944. Ten weeks prior to admission he had noted marked anorexia, nausea, and some vomiting; at the same time his upper abdomen was "sore to touch," especially on the right side. Two days after the onset of these symptoms he observed that his eyes were yellow. The jaundice deepened rapidly and was accompanied, almost from the first, by pruritus. The stools were light in color, the urine dark. Treatment by the local physician consisted of intravenous glucose and saline, together with bile salts and vitamin K by mouth. After the first week the nausea and vomiting disappeared and the appetite improved somewhat. In spite of this, however, there was a weight loss of approximately 30

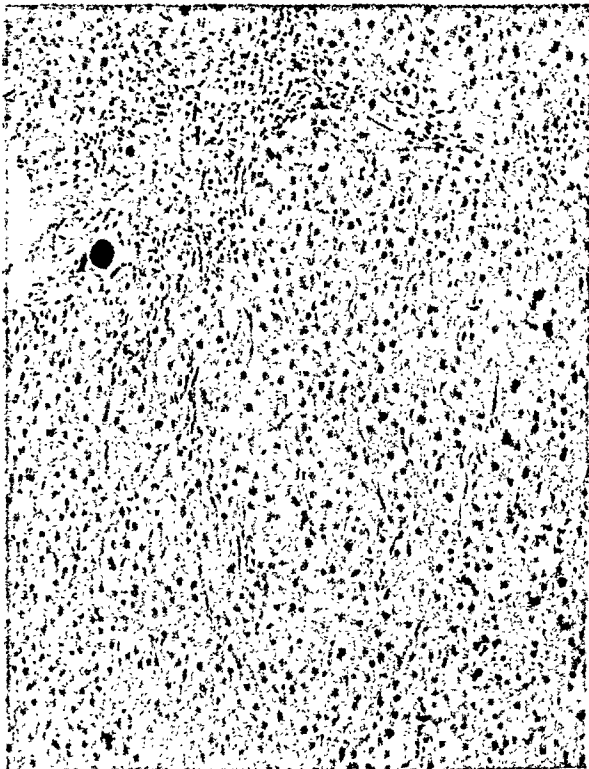
* Hykinone 4. mg. (Abbott Laboratories, Inc.)



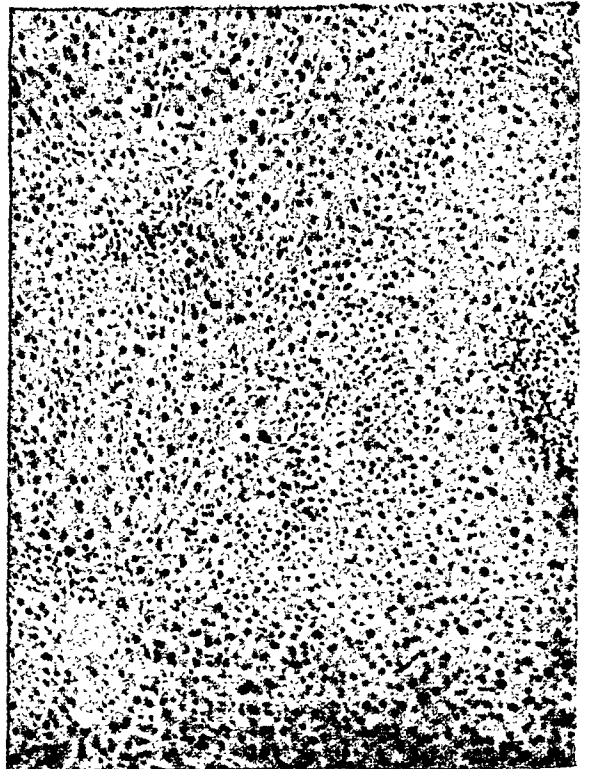
I A. Case 1. Cholangiolitic hepatitis. Microscopic appearance of liver biopsy secured on Nov. 29, 1944, during period of complete suppression of bile flow. The histology is surprisingly normal. Bilirubin staining is observed around the centers of the lobules. Hematoxylin and eosin $\times 90$.



I B. Case 2. Cholangiolitic hepatitis. Microscopic appearance of liver biopsy secured during febrile period shown in figure 3. Bilirubin staining of central lobular cells with occasional bile thrombi. Mild periportal cellular infiltration. Hematoxylin and eosin $\times 90$.



I C. Case 3. Cholangiolitic hepatitis with probable early cirrhosis. Microscopic appearance of liver biopsy secured 5 months after the onset of jaundice. Increase in portal connective tissue and mild lymphocytic infiltration. Multi-nucleated liver cells are common. Hematoxylin and eosin $\times 110$.



I D. Case 6. Cholangiolitic hepatitis. Microscopic appearance of liver biopsy secured at operation 5 months after onset of jaundice. Moderate periportal lymphocytic infiltration. No fibrosis. Some multi-nucleated liver cells. Central bilirubin staining. Hematoxylin and eosin $\times 90$.

pounds in the 10 weeks prior to admission. Further history was obtained that about one month before the onset of the above symptoms and jaundice, the patient was on a house party with eight other persons, including his wife. One of the other women in the group was mildly jaundiced and sufficiently ill to consult a physician in a small town near the summer home where the party was in progress. Of the other eight persons, four including the patient and his wife, subsequently became jaundiced. The wife's jaundice, however, disappeared in about 10 days, after which she recovered rapidly. The course of the disease was similarly mild in the others, except for the patient whose jaundice, as already noted, deepened progressively. In addition to the five persons in the group who became ill, it was determined that the small son and the sister of one of the jaundiced women later developed nausea, vomiting and icterus of relatively brief duration. It was of interest that the patient's daughter did not become sick or jaundiced.

Examination in the hospital revealed a well developed, deeply jaundiced, emaciated white male. The weight was 119 lbs. There was no temperature elevation, either upon admission or later. The blood pressure was 110 mm. Hg systolic and 60 mm. diastolic, pulse 56, regular rhythm. A mild fetor hepaticus was noted on the breath. The liver edge was easily palpable in the right mid-clavicular line at the level of the umbilicus. The spleen was barely palpable. No spider nevi were observed. There were many excoriations. Mild edema of the ankles was present.

The hemoglobin on admission to the hospital was 8.8 gm. per 100 c.c., the red blood cells 3,250,000 per cu. mm. Within a week the hemoglobin had fallen further to 7.1 and the erythrocytes to 2,850,000. The leukocytes ranged between 6100 to 11,200 with from 50 to 71 per cent neutrophils. Routine urinalysis revealed nothing abnormal except for the presence of bilirubin. The results of the composite liver function study are shown in figure 5. This revealed very little evidence of hepatic functional derangement, the only changes being in the failure of hippuric acid to appear in the urine after intravenous sodium benzoate, together with the lack of any elevation of cholesterol in spite of a marked regurgitation jaundice (1' bilirubin of 18.8 mg. with large amounts of bilirubin in the urine; pruritus). It is of interest that the total cholesterol value rose appreciably as the patient improved and as the jaundice diminished. In table 1 the serum cholesterol values are correlated with the serum bilirubin values and with those for the Ehrlich reaction in urine and feces. The intake of food was exceptionally good, ranging from 2500 to 4000 calories per day, not including 400 calories contributed by 1000 c.c. of 10 per cent glucose in distilled water which was given daily throughout the entire hospital stay. This solution contained 25 units of crystalline insulin which was included not with the idea of improving utilization of glucose, but because the administration of this mixture has been noted, in certain instances, to be followed by an increased appetite. During this entire period the patient received the low fat "liver" diet as described in the foregoing. A whole blood transfusion of 500 c.c. was given on Oct. 28, 1944, Nov. 21, 1944 and Nov. 26, 1944. At the time of discharge the hemoglobin was 16.7 gm. per 100 c.c. and the erythrocytes were 5,060,000 millions per cu. mm.

Liver biopsy was carried out in this instance on October 17, about 11 weeks after the onset of jaundice and just after completion of the liver function study shown in figure 5. The amount of liver obtained was relatively small, representing portions of but three lobules. Bilirubin staining was prominent, especially toward the periphery of the lobules. Quite a number of multinucleated liver cells were seen in the same areas. There was no necrosis, leukocytic infiltration, fibrosis or bile duct proliferation.

This patient was last seen on December 12, 1944, at which time he felt very well, although mild icterus was still evident. His appetite was good. The liver and spleen were not palpable.

Case 5. E. L., housewife, aged 51. The patient was admitted to the Medical

Service of the University Hospital on September 15, 1944. Her illness commenced with nausea and vomiting about July 4, 1944. At this time she felt cold and thought she had some fever, but there were no definite chills. Within a few days she became jaundiced and noted that the urine was dark and the stools light in color. The jaundice deepened and was associated with itching from the outset. There was no pain at any time, nor any history suggestive of gall stones. With the onset of nausea and vomiting a marked anorexia developed, especially characterized by distaste for fatty foods. The patient suffered a weight loss of 20 pounds prior to admission to the hospital. She stated that the jaundice and itching had become somewhat less but that the vomiting persisted.

TABLE I

Laboratory Data Relating to Jaundice and Serum Cholesterol in Case 4 (V. E., Male, 29)

Date	Ehrlich units Urine 2-4 p.m. sample	(urobilinogen) Feces (per 100 gm.)	Serum bilirubin in mg. per 100 c.c.		Serum cholesterol in mg. per 100 c.c.
			1'	Total	
10-12-44	0	16.8	18.8	34.6	183
10-16-44	0				
10-17-44	0				
10-19-44	0				
10-23-44	0.3				
10-27-44	0.9	9.6	10.1	18.3	
10-28-44					
10-30-44	1.0				
10-31-44					
11-1-44	3.8				
11-2-44	3.7	56.0	5.4	8.8	182
11-3-44	0.8				
11-6-44					
11-9-44	0.9				
11-14-44	1.0				
11-17-44		7.20	4.2	7.0	225
11-19-44	2.3				
11-20-44	2.09				
11-21-44	1.4				
11-22-44	1.5				
11-23-44		88.0	2.4	2.9	330
11-24-44	2.4				
11-27-44	2.2				
11-28-44					
11-29-44	1.0				
		160.0	0.9	2.1	312
		104.0			
					289

Examination revealed moderate jaundice with numerous excoriations of the skin. The liver edge was easily palpable 1 to 2 cm. below the right costal margin. It was not tender. The spleen was not palpable. Examination of the blood revealed a hemoglobin of 9.45 gm. per 100 c.c., erythrocytes 4,090,000, leukocytes 5050 to 8350 with from 52 to 79 per cent neutrophils, usually less than 60. The sedimentation velocity was 64 mm. in 60 minutes. The results of the composite liver function study are shown in figure 6. This reveals distinct, although variable, evidence of functional derangement in the presence of regurgitation jaundice; (bilirubinuria and increased 1' serum bilirubin). It may be noted on the basis of the feces urobilinogen, that the element of obstruction or exclusion of bile from the intestine was relatively slight. The stools at this time, of course, were no longer acholic in appearance.

Liver biopsy was done on Oct. 3, 1944, at the time of peritoneoscopy, using a modified Silverman needle as described elsewhere.²⁶ The appearance of the surface of

[illegible]

continue rest, to adhere to the "liver diet" and to take vitamin B complex, two capsules three times daily. She returned on November 1 stating that she felt very well. The liver and spleen were not palpable. There was still slight icterus, however, and if anything, the serum bilirubin had risen slightly: 1', 1.2 mg.; total, 2.8 mg. per 100 c.c. The patient was again seen on November 29 still feeling very well but slightly jaundiced. She was readmitted to the hospital February 6, 1945. At this time she still exhibited a mild jaundice. Pruritus had become severe and the patient's appetite was poor. Physical examination failed to reveal any appreciable change; the liver was not enlarged, the spleen was not palpable. Neither palmar erythema nor spider nevi were seen. Roentgen-ray examination of the esophagus failed to reveal any evidence of varices. A composite liver function study (see figure 7) revealed little change

Case 6. P. N., male, aged 69, laborer. The patient was admitted to the Medical Service of the University of Minnesota Hospital on February 4, 1944. He complained principally of intense pruritus; this had commenced in September, 1943, and gradually increased in severity. Jaundice was noted first in November. It was painless in onset and had gradually increased in intensity. The patient denied any history of abdominal pain, nausea or vomiting in relation to the present illness. There was no

[illegible]

history of alcoholism, no exposure to known hepato-toxins, nor contact with other cases of jaundice. The appetite had remained good; nevertheless, a 10 pound loss of weight had occurred over a six month period. A review of the past history revealed nothing of significance.

Physical examination revealed a well developed and well-nourished male of the stated age. Moderately severe jaundice was visible; the entire body was involved by excoriations secondary to the pruritus. No other abnormalities were detected. Repeated subsequent examinations of the abdomen failed to reveal the presence of an enlarged gall-bladder. The liver and spleen were not enlarged. The routine examination of the urine disclosed no abnormality other than the presence of bilirubin.

The patient was transferred to the Surgical Service and an exploration of the common bile duct was performed by Dr. Richard Varco. The gall-bladder was small and not distended. The common bile duct was not dilated. The duct was explored and found to be patent throughout its course. A T tube was inserted into the duct and brought to the surface through a stab wound. Two biopsies of the liver were made.

Postoperatively the amount of bile draining to the outside averaged only about 50 to 75 c.c. daily. The degree of jaundice remained essentially the same as it had been preoperatively, and it is worthy of note that the pruritus persisted.

Study of the biopsy of the liver (plate 1d) was reported by Dr. J. S. McCartney to show no increase in portal connective tissue. An excessive number of leukocytes was present in the portal spaces. Scattered bile thrombi were noted, mostly in the regions of the centers of the lobules. The central liver cells were pigmented by bilirubin. Some multinucleated cells were noted. In general the preservation of the normal structure was surprising.

One month after the common duct exploration, a cholangiogram was performed. This revealed good filling of the common duct and the gall-bladder. Some of the intrahepatic branches of the bile ducts were visible. Good drainage into the duodenum was apparent in 15 minutes. The serum bilirubin at the time of the cholangiogram was 6.9 mg. per 100 c.c. of which 5 mg. was the prompt direct (1') reacting bilirubin. Stool examination at this time revealed 30 Ehrlich units per 100 grams. Analysis of a four day collection of feces immediately prior to this had shown 21 mg. of urobilinogen per day. At the time of discharge from the hospital on April 15, 1944, the patient appeared much the same as when first observed, the pruritus and icterus persisting. He was instructed to continue rest and the "liver" diet at home and to return to the out-patient clinic for follow-up examinations. The T tube was removed in May, 1944, three months after its insertion; jaundice was still evident. By August, 1944, the visible jaundice had disappeared although the serum bilirubin value was still 1.9 mg. per 100 c.c., of which 0.6 mg. was the 1' type. By September, 1944, the serum bilirubin was normal, the pruritus had largely disappeared and the patient felt well.

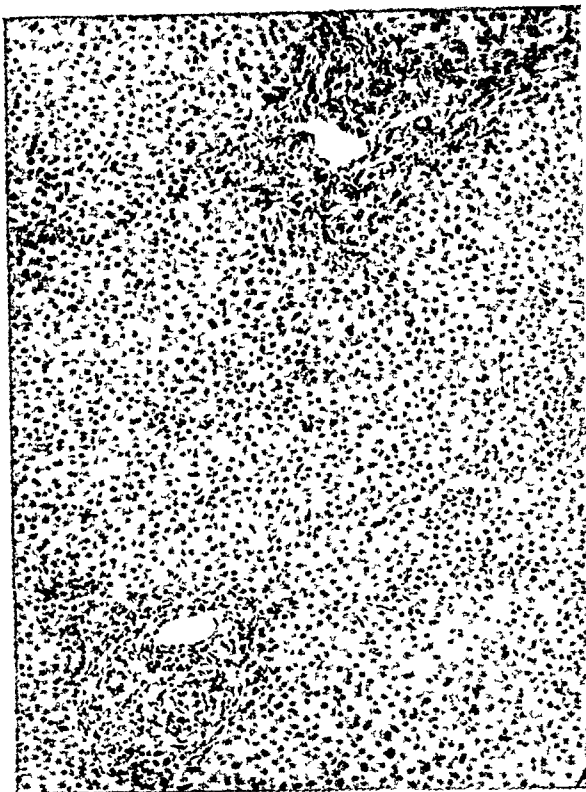
This patient had pruritus lasting one year (September, 1943, to September, 1944) and had been jaundiced for 10 months (November, 1943, to August, 1944). During all of this time he felt fairly well, was free of pain, had a good appetite and lost relatively little weight. No benefit was derived from the surgical exploration and the external biliary drainage insofar as the patient was concerned. This case truly bears out the statement made by Rolleston²⁰ 40 years ago, "Occasionally cases, which begin like ordinary catarrhal jaundice and eventually clear up, hang fire and last for months." It is true that the onset in this instance was somewhat unlike the ordinary case in that the pruritus was present for about two months before the jaundice was noted.

Case 7. F. R., male, aged 47. This patient came under observation in June, 1943, through the courtesy of Drs. J. E. Meyer and M. C. James of Columbus, Nebraska. His complaints were those of pruritus, mild jaundice and fatigability. The pruritus had been present for about four years. It was relatively mild in character and had not caused much discomfort. Jaundice was first noted in October, 1942, when the patient consulted his physician for removal of a xanthoma of the eyelid. Because of the persistence of the jaundice, an exploratory laparotomy was performed and the gall-bladder was drained. No stones were found in the gall-bladder or in the extrahepatic biliary tract. Biopsy of the liver was performed. This was reported as indicating a hepatitis. Drainage of the gall-bladder failed to influence the jaundice or pruritus.

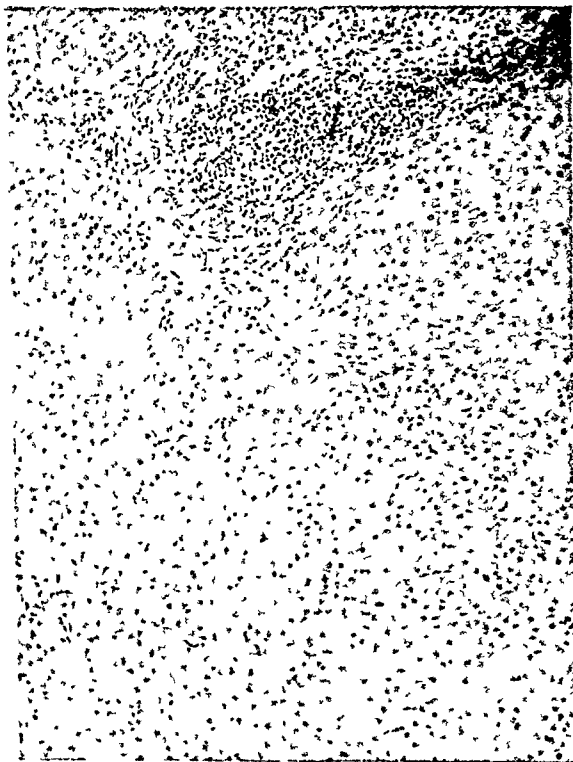
Physical examination in June, 1943, revealed a well developed, well nourished male of 47. Apart from a slight icterus there were no apparent abnormalities. Care-



II. A. Case 5. Cholangiolitic hepatitis. Microscopic appearance of liver biopsy secured during peritoneoscopic examination Oct 3, 1944. Relatively normal histology. Occasional bile thrombi, occasional multi-nucleated liver cells. Portal spaces and evidence of cholangiolitis not shown in this section. Hematoxylin and eosin $\times 110$.



II. B. Case 5. Cholangiolitic hepatitis and early cirrhosis. Microscopic appearance of liver biopsy secured at the time of operation (cholecystostomy) March 6, 1945. Portal lymphocytic infiltration and mild fibrosis. Bile duct proliferation and swelling. Multi-nucleated liver cells. Hematoxylin and eosin $\times 90$.



II. C. Case 8. Cholangiolitic hepatitis and early cirrhosis. Microscopic appearance of liver biopsy secured at operation in 1936. Marked periportal lymphocytic infiltration with mild increase in portal connective tissue and new bile ducts. Some of these are swollen and have atypical epithelium. Hematoxylin and eosin $\times 90$.



II. D. Case 8. Cholangiolitic hepatitis and cirrhosis. Microscopic appearance of liver biopsy secured at operation in 1945. The cirrhosis is seen to be well developed as contrasted with the appearance in 1936 (II C). Extreme portal fibrosis and lymphocytic infiltration; bile thrombi. Hematoxylin and eosin $\times 90$.

mal. No signs of necrosis or proliferation of liver cells can be made out. Conclusion: Early cirrhosis of the liver."

Case 8. C. Q., female, aged 48. This patient was first studied on the Medical Service of the University of Minnesota Hospitals between April 9, 1943, and June 1, 1943. In September, 1944, she was readmitted for a period of one week of observation. Her third admission began April 16, 1945; she was discharged on June 2, 1945. At the time of the first admission the patient complained of weakness, epigastric discomfort, and occasional bouts of diarrhea. Review of her history disclosed that she had had jaundice more or less continuously since the age of 15. This was characterized by recurrent episodes of deeper jaundice, with dull aching right upper quadrant pain. The patient did not use alcohol in any form; her dietary intake was normal.

In 1912 this patient, then 15 years of age, was severely jaundiced during an illness which was characterized by high fever and a prolonged period of disability. Her sister also had jaundice at that time although her symptoms were milder in nature. As nearly as can be ascertained this illness was a severe form of infectious hepatitis (acute catarrhal jaundice). In 1932 during her fourth and last pregnancy the patient was more markedly jaundiced during the last seven months; anorexia and nausea were prominent. In 1936 she consulted Dr. M. O. Oppegard of Crookston, Minnesota, who has kindly made available his observations and surgical findings. Examination at this time revealed that the liver was much enlarged and firm; splenomegaly was noted but there was no evidence of ascites. Roentgen-ray studies revealed a non-functioning gall-bladder. After a period of observation cholecystectomy was decided upon, as offering the patient some hope of relief of the recurrent discomfort. At operation Dr. Oppegard found an enlarged liver exhibiting a definite hobnailed surface. The spleen was enlarged to about three times its normal size. The gall-bladder was found to be thick walled and firmly adherent to the fossa; it contained no stones. A biopsy of the liver was made and a cholecystectomy was performed. The patient made an uneventful recovery and appeared for a time to be relieved of some of her distress. The liver biopsy section was made available to us through the courtesy of Dr. Kano Ikeda, Pathologist at the Miller Hospital, St. Paul, Minnesota. A photomicrograph is shown in plate 2c.

One year later, in 1937, the patient was subjected to a second operation at which a Talma-Morrison omentopexy was performed by Dr. J. F. Malloy at Thief River Falls, Minnesota. The report of this operation was made available to us by Dr. Edward Bratrud of Thief River Falls. It was found that the liver was enlarged, the right lobe extending to the iliac crest; the spleen was enlarged to one and one-half times the normal size. The patient's recovery was uneventful after this operation. She continued, however, to have varying degrees of jaundice. The patient was able to perform most of her household duties, being incapacitated only during periods of more marked jaundice and distress.

In 1943, during the first period of study by us, the outstanding features on physical examination were the massively enlarged liver and the presence of minimal icterus. Ascites was not demonstrable, nor were any spider nevi observed. A faint but definite fetor hepaticus was repeatedly discernible; this was confirmed by several observers. A clinical diagnosis of Hanot's cirrhosis was made. Numerous liver function tests were carried out in serial fashion at this time. The initial observations are shown in figure 10. These reveal obvious evidence of hepatic functional impairment. During this first period of hospitalization, the patient received the "liver diet" and supplements of choline and cystine for a period of six weeks. Although subjective improvement occurred, no significant change in liver function was noted as measured by serial tests. She was allowed to return home on the same diet, but without the choline and cystine. The diet was supplemented by yeast powder and vitamin B complex. This regime was followed for the ensuing year; frequent clinic visits permitted further clinical and laboratory observations.

[illegible]

The patient was treated by means of bed rest; she received a diet containing carbohydrate 350 grams, protein 150 grams, and fat 88 grams. This is an increase of 38 grams of fat per day over the previously mentioned liver diet and represented an increased allotment of butter and cream. Recent observations have convinced us that the increased palatability of such a diet more than outweighs any possible deleterious effect of the increased fat. In addition to vitamin supplements, both orally and parenterally, the patient received 5 grams of methionine in a liter of 10

per cent glucose as a daily intravenous infusion. No appreciable change in her condition was noted after two weeks. The pruritus was well controlled, however, with 1 mg. of a di-hydroergotamine preparation (DHE-45*) given by injection every third day. No untoward effects were noted in this or in other patients in whom this product has been used.

Since the remote possibility of a common duct calculus or an inflammatory stricture could not be excluded surgical exploration was requested. On May 8, 1945, Dr. Richard Varco explored the biliary tract; the liver was definitely hobnailed and had the gross appearance of a cirrhosis. The common bile duct was not dilated, no stones were encountered and a probe was readily passed into the duodenum. External biliary drainage was established by means of a catheter inserted into the remaining stump of the cystic duct. A biopsy of the liver was secured.

The patient experienced prompt relief of her pruritus. She was released from the hospital on June 1, 1945, to be followed in the out-patient clinic.

Dr. J. S. McCartney's reports of the histologic findings in the two liver biopsies from this case, are as follows:

1936 (Plate 2c). "This piece of liver tissue shows portions of many lobules. There is a definite increase in connective tissue and new bile duct proliferation in the portal spaces, but no evidence of fatty metamorphosis is seen. The portal cellular infiltrate is largely composed of lymphocytes and plasma cells, the latter being especially prominent." Some of the cholangioles appeared swollen and had atypical epithelium. Conclusion: Early cirrhosis of the liver.

1945 (Plate 2d). "This piece of liver tissue shows portions of many lobules. The lobules vary greatly in size. No central veins are seen. The increase in the portal connective tissue is quite marked with only a minimal amount of new formation of bile ducts and a moderate degree of leukocytic infiltration. The increased portal tissues are quite vascular. In the liver lobules themselves there are fairly numerous bile thrombi which are in part centrally situated and in part at the periphery." Conclusion: Cirrhosis of the liver.

The patient returned to the hospital on July 15, 1944 because of the appearance of hematemesis for the first time. It was learned that four days earlier, following irrigation of the catheter draining the common bile duct, she had developed chills, fever and an increasing jaundice. Vomiting of blood occurred on four occasions on the day of admission. The blood loss was severe and the patient lapsed into a comatose state shortly after admission. Following transfusions of whole blood and infusions of plasma she exhibited a rather remarkable response and regained consciousness. The bleeding recurred, however, and the patient died on July 27, 1944.

At autopsy, the gastrointestinal bleeding was shown to be due to esophageal varices. The liver weighed 3050 grams. The external and cut surfaces were coarsely granular and greenish in color. The common bile duct was patent throughout its course, and was not dilated. The spleen weighed 390 grams and was obviously congested. The remainder of the examination showed nothing of note. Microscopically the sections of the liver revealed marked portal fibrosis with a considerable number of newly formed bile ducts in the portal spaces. The histological picture was essentially the same as that of the biopsy obtained a few months earlier (Plate 2d). Dr. McCartney's conclusion was "advanced cirrhosis of the liver." This was certainly indistinguishable microscopically from an ordinary atrophic or classical Laennec type of cirrhosis, yet it may be emphasized that even after so many years' duration, the liver weighed 3050 gm., and this increase in weight was not due to fat, but rather to connective tissue and new bile ducts, at least in the main.

* Kindly made available to us by Sandoz and Co.

DISCUSSION

The above cases have been selected from our material because they illustrate a number of points regarding prolonged hepatitis which we believe are deserving of more emphasis. The concept of a variety of hepatitis in which the manifestations, at least at some stages of the disease, are wholly or mainly those of regurgitation jaundice, with little or no disturbance of liver cell function, is clearly upheld by our experience. Cases 1 and 6 in the present group are particularly illustrative. In case 6 it was established at operation and by subsequent choledochogram, that there was no extrahepatic biliary tract obstruction, yet the liver was not enlarged, the liver cells appeared normal and the liver cell function prior to operation, as determined by the composite liver function study, was surprisingly normal. The paucity of histologic change in this liver was striking, and this was true, in fact, of others in the group as well. We are not impressed by the tangible gross or microscopic evidence of mechanical biliary obstruction within the liver and since we do not believe that these are cases of choledochitis or extrahepatic obstruction, the exact mechanism of production of regurgitation jaundice remains to be determined. There is rather widespread belief that there is "intrahepatic biliary obstruction" due either to periportal cellular accumulations, to bile thrombi, or to actual increase in size of the liver cords.^{5, 6, 31, 32} These factors in varying importance have been believed to serve in a mechanical fashion to obstruct bile flow within the bile capillaries or small bile ducts. When such changes are prominent there is no reason to doubt their rôle in hindering the outflow of bile, but in some cases, at least, neither cellular accumulation, bile thrombi, nor liver cord swelling are at all impressive and one wonders, therefore, whether an entirely different mechanism of regurgitation of bile may not obtain. On the basis of existing evidence, the first possibility here is that of leakage or diapedesis of bile because of increased permeability of the cholangioles* due to injury by the causative agent. This might be thought of as somewhat analogous to the leakage of glomerular filtrate back through the damaged tubules of the kidney in mercury bichloride poisoning, with resultant oliguria and azotemia. Experimental studies have, in fact, indicated that poisons such as toluylenediamine produce jaundice in animals by virtue of causing an increased permeability of the bile capillaries,^{34, 35, 36} particularly the ampullae between the capillaries and the primary bile canaliculi, the area designated by Aschoff as the "Achilles heel" of the biliary system.³⁷ In obstructive jaundice actual rhexis or mechanical rupture of the ampullae has been described.³⁸ In either event bile is returned to the blood, in the earlier stages at least, mainly via the lymph,^{35, 38, 39, 40, 41, 42} and regurgitation jaundice is thus brought about. The idea of regurgitation of bile through injured, although not necessarily broken, biliary radicles was advanced much earlier, however, than the

* This term is used broadly to include the finer biliary radicles, especially the ampullae of the bile capillaries and the primary bile canaliculi in the portal spaces of the liver.

studies of Ohno and his associates,³⁶ which have just been referred to. Minkowski⁴³ and Naunyn⁴⁴ employed the terms "parapedesis" and "cholangie," respectively, to express the belief that the bile was going the wrong way, i.e., back into the blood, even in cases where there was no definite evidence of biliary obstruction or of cholangitis, although the terms were rather loosely employed, especially "parapedesis" by Minkowski, who evidently related it to regurgitation jaundice generally. The same is true of the term "paracholie" as suggested by Pick.⁴⁵ Umber, a pupil of Naunyn's, continued to champion the term "cholangie,"⁴⁶ and it is significant that he described cases of jaundice to which he applied this term even though evidence of biliary obstruction or of any cholangitic change, was entirely lacking, cases in other words quite similar to those which have just been described. It is quite true that the terms "paracholie" and "cholangie" as employed by Minkowski and Naunyn, respectively, do not insist upon a return to the blood of bile constituents which have actually been within the bile capillaries, but would include a possibility which cannot be excluded with certainty, i.e., that of excretion of these constituents by the liver cells into the lymph spaces of Dissé rather than into the bile capillaries. At the present time there is no basis for a choice between these two possibilities.

Eppinger,⁵ and more recently Urteaga⁴⁷ have emphasized their belief that bile thrombi are of major significance in the production of jaundice in hepatitis on the basis of actual obstruction of the bile capillaries or canaliculi. While there is no reason to doubt that bile thrombi may be of considerable importance, if present in large enough numbers, we believe that they represent a secondary phenomenon since in some instances, at least, even in the presence of marked regurgitation jaundice, they are not sufficiently numerous to be impressive as the primary factor in the production of jaundice. Their occurrence would fit well, however, with the concept of regurgitation of bile by leakage through damaged bile capillaries or ampullae, since it is logical to assume that in the course of such a "diapedesis" of bile, relatively more water and less solid would leak through into the spaces of Dissé, with the result that whatever bile remained in the capillary would tend to become inspissated, thus favoring the formation of bile thrombi.

The question comes up as to whether in the prolonged cases of hepatitis in which relatively little evidence of reduced hepato-cellular function is observed, there may, nevertheless, have existed at an earlier stage of the disease a considerable liver cell damage and altered function, which by the time the patient is first studied has largely healed leaving nothing but the factor of bile regurgitation. This question has been answered affirmatively by Turner and his associates¹⁸ and by Neefe, Stokes, Reinhold, and Lukens^{21a} although in neither instance on the basis of serial histological examinations. The marked increases of urine urobilinogen which are observed in the early stage of epidemic or sporadic hepatitis⁶² can only be interpreted as an evidence of hepatocellular damage. Mild increases were observed, later in the disease,

in the majority of the present cases even though other evidence of disturbed liver function was lacking or minimal. Eppinger⁵ pointed to the early presence of urobilinogenuria and reduced galactose tolerance, regarding these as evidence of hepatocellular injury. The latter in particular was correlated with evidences of so-called "serous inflammation," other signs of which were: transitory hemoconcentration, widening of Dissé's space and edema of the interacinar spaces. The recent study of Axenfeld and Brass⁴⁸ indicates a regular injury of the liver cells particularly in the centers of the lobules, during the first few days of the disease. They also noted evidence of "serous inflammation" such as observed by Eppinger. Proliferation of reticuloendothelial cells and rapid regeneration of liver cells, first by mitosis, later amitosis, was described as occurring regularly. Histologic study of the present liver biopsy material often revealed multinucleated liver cells suggesting regeneration secondary to injury (see Plate 1c, 1d, and 2a) as recently stressed by Lucké.⁴⁹ Case 2 in particular illustrates that whatever histologic evidence of liver cell damage exists in these cases may disappear relatively early in the course of the disease, and even while the infectious activity is still marked, as evidenced by the hyperpyrexia at a time when the liver biopsy revealed strikingly little evidence of disease. This type of case suggests that in some instances, at least, a severe functional derangement of the cholangioles and to a lesser extent of the liver cells may be present though not microscopically apparent. In cases 5 and 8 there was a minor evidence of cholangiolar injury, consisting of swollen, atypical epithelium. Case 4 in the present group provides ample evidence that the prolonged, or cholangiolitic type is or can be produced by the same infectious agent responsible for the ordinary, briefer (hepatocellular) variety. Axenfeld and Brass observed various transitions, in cases of epidemic hepatitis, from the initial diffuse hepatocellular injury to the picture of cholangiolitic hepatitis, which they regard simply as the subacute or subchronic stage of the disease.

The prominence of pruritus in the prolonged form of hepatitis deserves further mention. While final proof is lacking that the bile acids or their salts are responsible for pruritus, there can be little question that this symptom is due to a return of some constituent of bile to the blood, and hence that it may be regarded as a very characteristic manifestation of regurgitation jaundice, with relatively normal hepatocellular function. In case 6 of the present series, the occurrence of itching for two months prior to the recognition of jaundice indicates some degree of selectivity in this regurgitation or postulated increase in permeability of the cholangioles, but in this connection it may be emphasized that considerable elevations of serum bilirubin together with mild bilirubinuria may occur without the patient's cognizance. The prompt disappearance of pruritus in cases 5 and 8, following external biliary drainage, is worthy of note. In these instances the bile drainage was considerable, while in case 6 in which it was scanty, the pruritus did not disappear. Here one would have to assume that most of the bile salts being

formed by the liver cell and excreted into the bile were returning promptly to the blood without an enterohepatic circulation, while in cases 5 and 8 the disappearance of itching may well have been due to interruption of the enterohepatic circulation of bile salts.* This would imply, merely, a different degree of injury of the cholangioles in the two cases, in favor of which was the more marked regurgitation jaundice in case 6.

The problem of relationship of hepatitis to cirrhosis of the liver is an exceedingly important one, especially in view of the marked increase in incidence of hepatitis during the war, as discussed at the outset. The majority of investigators favor the view that some cases of hepatitis become chronic in nature and develop diffuse cirrhosis.^{5, 6, 12, 13, 48, 50, 51, 64} This is not to be confused with the so-called toxic or postnecrotic cirrhosis, or healed acute yellow atrophy,^{52, 53} the occurrence of which has been generally accepted as a sequel of a very severe hepatitis, a relationship especially well documented by Bergstrand.⁵⁴ Lucké⁵⁵ while accepting the latter type, is not convinced that any relationship exists between epidemic or sporadic hepatitis or so-called catarrhal jaundice on the one hand, and diffuse cirrhosis of the liver on the other. Nevertheless, evidence has been accumulating for a number of years which strongly supports such a relationship. Jones and Minot,⁵⁰ in a thorough study of catarrhal jaundice reported in 1923, refer to the development of cirrhosis after several months of jaundice. In speaking of this transition Jones and Minot expressed the following belief: "Serious complications outside of the biliary tract appear to be rare. The term 'complication' has been used in the above discussion in reference to certain untoward occurrences observed in the course of apparently typical cases of infectious jaundice. The advisability of such a term may be questioned by some who may believe that the original diagnosis is at fault. We believe, however, that the above cases warrant the use of the term 'complication.' The first two cases with the infectious cirrhosis occurred in the same family within a week of each other and ran an identical course. The last two cases developed in the midst of well-recognized epidemics, and at the start differed in no way from other cases observed in these epidemics. The final outcome alone differed from the results seen in the other epidemic cases. The serious results reported occurred, we believe, in well authenticated cases of infectious jaundice, were not coincidental, and were probably complications of the original infection."

As Eppinger⁵ points out, the usual case of acute hepatitis recovers completely within a few weeks but there are cases in which the jaundice does not disappear, and in which after six months or a year the clinical picture is that of "biliary" cirrhosis, i.e., jaundice, enlarged firm liver, spleen commonly palpable and firm, ascites usually absent. Eppinger would reserve the design-

* The possibility of eliminating pruritus in cases of longstanding non-obstructive jaundice, by partial interference with the enterohepatic circulation, was suggested to us by Dr. Richard Varco.

nation biliary cirrhosis for those cases in which so-called "catarrhal" jaundice persists and gradually exhibits more and more of the features of cirrhosis. From a clinical standpoint this form of cirrhosis is most compatible with that originally described by Hanot.⁵⁶ According to Karsner⁵³ Hanot's cirrhosis is probably comprised by the conditions described by Lichtman,⁶ Klemperer⁵⁷ and Rössle,⁵⁸ under the following designations, and, according to Karsner, the following histologic differences:

Lichtman: Non-obstructive cholangitic biliary cirrhosis	{ Evidence of cholangitis and fibrosis in portal spaces.
Klemperer: Chronic intrahepatic obliterating cholangitis	
Rössle: Cholangiolitic or cholangiotoxic cirrhosis	Intralobular fibrosis and cellular infiltration.

Karsner⁵³ mentions an example of the latter variety which he studied. This was in a male, 32, a periodic alcoholic, who had had repeated attacks of what appeared to be acute hepatitis over the course of 10 years. There were jaundice, enlargement of the spleen and liver but no ascites, in other words a clinical picture corresponding with Hanot's cirrhosis. At autopsy the liver weighed 4100 gm. and exhibited "cholangiolitic biliary" cirrhosis. If one can judge from the microphotographs in Karsner's paper, this was not a fatty cirrhosis. It may be noted again, with respect to the question of repeated attacks of hepatitis, that these are well known and that one attack does not necessarily confer immunity. The question is whether in such instances one is dealing with a continuous chronic virus infection having latent periods and exacerbations, whether a re-infection has occurred, or whether, after the subsidence of the virus infection, the progression of the disease is due to inability of the once damaged liver to inactivate or detoxify some injurious substance, possibly of metabolic origin. In case 8 of the present series, certainly the most remarkable insofar as the question of transition of infectious hepatitis to cirrhosis is concerned, the history indicated a continuous chronic disease of 34 years' duration following the initial acute episode. As a striking instance of individual variation it may be noted again that the sister, who had also suffered from infectious jaundice 34 years previously, recovered completely and has had no further jaundice nor manifestations of liver disease. Bloomfield⁵¹ was particularly impressed with the concept of a latent chronic form of hepatitis gradually progressing to a clinically manifest cirrhosis of the liver, and cited numerous cases apparently exhibiting such transitions. Steigmann and Popper³¹ likewise regard chronic hepatitis and cirrhosis as identical and describe two cases of unusually prolonged acute hepatitis in which laparotomy with biopsy revealed clear cut evidence of developing cirrhosis. The histologic changes described agree well with the concept of a cholangiolitic cirrhosis which is perhaps the best term to designate briefly the type of cirrhosis developing after hepatitis. Axenfeld and Brass, in an extensive study of epidemic and sporadic hepatitis carried out with the aid of liver biopsy and reported in 1942,¹⁸ conclude that cholangiolitic hepatitis

represents a subacute or sub-chronic stage of the disease, and that in some instances definite transition to cirrhosis of the liver is observed.

Bloomfield's cases, in the main, were instances of ordinary portal cirrhosis and the majority were in alcoholics, only 10 per cent giving a history of a previous episode of jaundice. In Patek's study of cirrhosis^{5a} the incidence of a previous episode of jaundice was but 5 per cent, in other words approximately that of the population at large. Most of Patek's cases, like Bloomfield's, were chronic alcoholics, so that it may be assumed that a fatty liver and hence an intermediate fatty cirrhosis was the usual sequence of events in the development of the portal or atrophic cirrhosis which was observed. It must be emphasized that there are probably at least two mechanisms by which a so-called hypertrophic cirrhosis may gradually become atrophic: (1) The large fatty cirrhosis which loses fat and gains scar tissue, with concomitant shrinking. (2) The large relatively non-fatty cholangiolitic cirrhosis in which, initially, there are periportal lymphocytic foci, bile thrombi, bile duct proliferation, hyperplasia of reticular cells, and beginning fibrosis; later extensive fibrosis with resultant hardening and shrinking. Lichtman⁶ records an excellent example of the latter type. Fatty cirrhosis is regarded as probably not related to hepatitis, but rather to chronic dietary deficiency often on the basis of alcoholism; the non-fatty, cholangiolitic cirrhosis is believed, at least in many instances, to be the sequel to infectious hepatitis. It is regarded as very doubtful that the end stages of the two diseases can always be distinguished with certainty on anatomic or histologic grounds. This is intended to imply, simply, that what may first present as "hypertrophic" biliary, or Hanot type of cirrhosis may eventuate in an ordinary portal or atrophic cirrhosis. It is believed that the distinction of fatty or dietary cirrhosis from the non-fatty or cholangiolitic type may well have therapeutic implications at least in the earlier stages since there is every reason to believe that cholin-cystin or methionine, or a high protein diet would be more effective in the former than in the latter type.

It is not meant to imply that a cirrhosis secondary to hepatitis might not become fatty if the individual, because of anorexia, were on a deficient diet for a sufficiently long period. Conversely there is little doubt that by the use of lipotropic substances, much of the fat in an alcoholic or dietary cirrhosis may be mobilized with resultant shrinking of the liver. It is also not implied that fat, per se, causes cirrhosis of the liver, but only that a fatty liver represents the early stage of evolution of so-called alcoholic or dietary cirrhosis, in contradistinction to the non-fatty cholangiolitic hepatitis which is believed to represent the early stage in development of cholangiolitic cirrhosis.

In the foregoing we have emphasized the question of relationship between hepatitis and "biliary" cirrhosis because our own material lends support to such a concept. Cases 5, 7, and 8 have been selected as especially illustrative. In case 5 the manner of onset of the disease was indistinguishable from that of ordinary sporadic or epidemic hepatitis, although a history of definite

contact was not established. The improvement during the first hospital admission, with subsequent relapse, when correlated with the progression from hepatitis without cirrhosis (Plate 2a) to hepatitis with cirrhosis (Plate 2b), form a rather convincing picture of the development of cirrhosis in a case of prolonged hepatitis. We believe that case 7 likewise exemplifies this transition. Whether the initial hepatitis in either instance was identical with epidemic hepatitis is not known. The fully developed clinical picture in both of these cases was characterized by pruritus, regurgitation jaundice without ascites, enlarged liver and spleen, hypercholesterolemia and hyperphosphatasemia. This syndrome is suggestive of xanthomatous biliary cirrhosis, and in this connection we would emphasize, in agreement with Parkes-Weber,⁵⁷ that the entire clinical picture of this latter condition may be produced by, or exist in association with, a cirrhosis in which no xanthomata of the extra- or intrahepatic bile ducts are to be found at autopsy. A case of this type has recently been described by us.⁶¹ The question may be raised as to whether such instances are not late stages of a chronic cholangiolitic hepatitis with progressive cirrhosis. As Hanger and Gutman³² have shown, entirely similar chemical findings may be observed in the cholangiolitic hepatitis seen at times following arsphenamine therapy, so that there is little need of ascribing a marked hypercholesterolemia and hyperphosphatasemia to a metabolic error. One may well ask, on the contrary, whether certain forms of hepatitis and cirrhosis do not actually give impetus to an overproduction of these substances.

In the foregoing, we have emphasized the cholangiolitic type of hepatitis and its transition to a similar variety of cirrhosis. We do not mean to imply, however, that this is the only variety of transition, and in fact, we have seen a number of other instances in which cirrhosis followed infectious hepatitis, but in which the regurgitation jaundice of the cholangiolitic type, with its characteristic prints, hypercholesterolemia, and hyperphosphatasemia, was not present.

SUMMARY AND CONCLUSIONS

1. Certain cases of prolonged hepatitis exhibit normal or relatively normal hepatocellular function in the presence of marked regurgitation jaundice. The histologic changes often appear inadequate to account for the jaundice. These consist in the main of a varying amount of periportal lymphocytic infiltration, bilirubin staining of the liver cells especially in the centers of the lobules, and bile thrombi in variable number. In the absence of sufficient evidence of this type to indicate intrahepatic biliary obstruction, it is believed that the continued regurgitation of bile supports the concept of increased permeability (functional injury) of the cholangioles. This regurgitation is manifested by a prompt direct (1') hyperbilirubinemia, hypercholesterolemia, hyperphosphatasemia, and pruritus.

2. In some cases of epidemic hepatitis liver biopsy may fail to reveal

histologic evidence of any appreciable hepatocellular injury at a relatively early period of the disease, when infectious activity is still manifest. Since, in these cases, there is often some residual evidence of reduced hepatocellular function, it is believed that there was, initially, a more marked liver cell injury, and that the prolonged regurgitation jaundice simply indicates a more severe affection of the intrahepatic bile duct system than in the ordinary case.

3. The problem of the relation of prolonged or cholangiolitic hepatitis to the development of cirrhosis is considered; further examples representing transition from hepatitis to cirrhosis are discussed and the term cholangiolitic cirrhosis is suggested as being more appropriate and distinctive than "hypertrophic biliary cirrhosis." The prominence of regurgitation jaundice without ascites, but with pruritus, hypercholesterolemia and hyperphosphatasemia in this group of cases, is emphasized. The end stages of the cholangiolitic cirrhosis following prolonged hepatitis may be indistinguishable, anatomically, from ordinary atrophic or portal cirrhosis. The cholangiolitic type of hypertrophic cirrhosis is believed, however, to be distinct from the "hypertrophic" fatty cirrhosis which represents an intermediate stage between the fatty liver and the atrophic cirrhosis of chronic alcoholics or other conditions in which dietary deficiency is probably the most important etiologic factor.

BIBLIOGRAPHY

1. BAMBERGER: Cited by LEYDEN, E.: Beiträge zur Pathologie des Icterus, 1866, A. Hirschwald, Berlin, page 102.
2. VIRCHOW, R.: Ueber das Vorkommen und den Nachweis des hepatogenen, insbesondere des katarrhalischen Icterus, Virchow's Arch. f. path. Anat., 1865, xxxii, 117-125.
3. STOKES, WILLIAM: Clinical lectures on the practice of medicine, 1839, Fannin and Co., Dublin.
4. GRAVES, R. J.: Clinical lectures, 1864, Fannin and Co., Dublin, page 632.
5. EPPINGER, H.: Die Leberkrankheiten. Allgemeine und spezielle Pathologie und Therapie der Leber, 1937, Julius Springer, Wien.
6. LICHTMAN, S. S.: Diseases of the liver, gallbladder and bile ducts, 1942, Lea and Febiger, Philadelphia.
7. FLINDT, N.: Bemærkninger med Hensyn til den saakaldte katarralske Ikterus's Aetiologi og Genese, Bibliothek. f. Laeger, 1890, xxxii, 420-452.
8. EPPINGER, H.: Allgemeine und spezielle Pathologie des Ikterus, spezielle Pathologie und Therapy innerer Krankheiten, Kraus und Brugsch, 1923, Bd VI, Teil 3, Urban und Schwarzenburg, Berlin, p. 96-340.
9. LINDSTEDT, F.: Zur Kenntnis des Icterus catarrhalis, München. med. Wchnschr., 1923, lxx, 170-173.
10. KLEMPERER, P. KILLIAN, J. A., and HEYD, C. G.: The pathology of "icterus catarrhalis," Arch. Path., 1926, ii, 631-652.
11. GASKELL, J. F.: The changes in the liver in a fatal case of epidemic "catarrhal" jaundice, Jr. Path. and Bact., 1933, xxxvi, 257-262.
12. ROHOLM, K., and IVERSON, P.: Changes in the liver in acute epidemic hepatitis (catarrhal jaundice) based on 38 aspiration biopsies, Acta path. et. microbiol. Scandinav., 1939, xvi, 427-442.
13. DIBLE, J. H., McMICHAEL, J., and SHERLOCK, S. P. V.: Pathology of acute hepatitis: Aspiration biopsy studies of epidemic, arsenotherapy and serum jaundice, Lancet, 1943, ii, 402-408.

14. WITTS, L. J.: Some problems of infective hepatitis, *Brit. Med. Jr.*, 1944, ii, 739-743.
15. FINDLAY, G. M., and MARTIN, N. H.: Jaundice following yellow fever immunization, *Lancet*, 1943, i, 678-680.
16. FOX, J. P., MANSO, C., PENNA, H. A., and PARA, M.: Observations on occurrence of icterus in Brazil following vaccination against yellow fever, *Am. Jr. Hyg.*, 1942, xxxvi, 68-116.
17. Homologous serum jaundice, Memorandum prepared by Medical Officers of the Ministry of Health, *Lancet*, 1943, i, 83-88.
18. TURNER, R. H., SNAVELY, J. R., GROSSMAN, E. B., BACHANAN, R. N., and FOSTER, S. O.: Some clinical studies of acute hepatitis occurring in soldiers after inoculation with yellow fever vaccine, with especial consideration of severe attacks, *Ann. Int. Med.*, 1944, xx, 193-218.
19. NEEFE, J. R., MILLER, T. G., and CHARNOCK, F. W.: Homologous serum jaundice: A review of the literature and report of a case, *Am. Jr. Med. Sci.*, 1944, ccvi, 628-638.
20. OLIPHANT, J. W., GILLIAM, A. G., and LARSON, C. L.: Jaundice following administration of human serum, *Pub. Health Rep.*, 1944, lviii, 1233-1242.
- 21a. NEEFE, J. R., STOKES, J., JR., REINHOLD, J. G., and LUKENS, F. D. W.: Hepatitis due to the injection of homologous blood products in human volunteers, *Jr. Clin. Invest.*, 1944, xxiii, 836-855.
- 21b. NEEFE, J. R., STOKES, J., JR., and REINHOLD, J. G.: Oral administration to volunteers of feces from patients with homologous serum hepatitis and infectious (epidemic) hepatitis, *Am. Jr. Med. Sci.*, 1945, ccx, 29-32.
- 21c. NEEFE, J. R., STOKES, J., JR., and GELLIS, S. S.: Homologous serum hepatitis and infectious (epidemic) hepatitis. Experimental study of immunity and cross immunity in volunteers, *Am. Jr. Med. Sci.*, 1945, ccx, 561-575.
- 22a. HAVENS, W. P., JR., PAUL, J. R., and VAN ROOYEN, C. E.: Human transmission of infective hepatitis by oral route, *Lancet*, 1945, ii, 202.
- 22b. HAVENS, W. P., JR.: Experiment in cross immunity between infectious hepatitis and homologous serum jaundice, *Proc. Soc. Exper. Biol. and Med.*, 1945, lix, 148-150.
23. SIEDE, W., and LUZ, K.: Zur Aetiologie der Hepatitis epidemica, Weitere Untersuchungen zum Virusnachweis, *Klin. Wchnschr.*, 1943, xxii, 70-74.
24. OLIPHANT, J. W.: Infectious hepatitis: Experimental study of immunity, *Pub. Health Rep.*, 1944, lix, 1614-1616.
25. HAVENS, W. P., JR.: Infectious hepatitis in the Middle East: A clinical review of 200 cases seen in a military hospital, *Jr. Am. Med. Assoc.*, 1944, cxxvi, 17-23.
26. HOFFBAUER, F. W., EVANS, G. T., and WATSON, C. J.: Cirrhosis of the liver: With particular reference to correlation of composite liver function studies with liver biopsy, *Med. Clin. N. Am.*, 1945, 363-389.
27. WATSON, C. J., SCHWARTZ, S., SBOROV, S., and BERTIE, E.: Studies of urobilinogen. V. A simple method for the quantitative recording of the Ehrlich reaction as carried out with urine and feces, *Am. Jr. Clin. Path.*, 1944, xiv, 605-615.
28. DUCCI, H., and WATSON, C. J.: The quantitative determination of the serum bilirubin with special reference to the prompt reacting and the chloroform-soluble types, *Jr. Lab. and Clin. Med.*, 1945, xxx, 293-300.
29. ROLLESTON, H. D.: Diseases of the liver, gallbladder, and bile-ducts, 1905, W. B. Saunders and Co., Philadelphia, p. 659.
30. NAUYN, B.: Cited by F. Umber, refr. no. 46.
31. STEIGMANN, F., and POPPER, H.: Intrahepatic obstructive jaundice, *Gastroenterology*, 1943, i, 645-654.
32. HANGER, F. M., JR., and GUTMAN, A. B.: Postarsphenamine jaundice; apparently due to obstruction of intrahepatic biliary tract, *Jr. Am. Med. Assoc.*, 1940, cxv, 263-271.
33. ALTHAUSEN, T. L.: Functional aspects of regenerated hepatic tissue, *Arch. Int. Med.*, 1931, xlviii, 667-675.

34. HIYEDA, K.: Experimentelle Studien über die Pathogenese des Ikterus. Ueber die Entstehung des Toluylenediaminikterus, Beitr. z. path. Anat. u. z. allg. Path., 1927, lxxviii, 389-407.
35. ИТОИ, Т.: Experimentelle Studien über die Pathogenese des Toluylenediaminikterus, Beitr. z. path. Anat. u. z. allg. Path., 1931, lxxxvi, 488-516.
36. OHNO, Y.: Experimentalstudien zur Ikterusgenese, München. med. Wchnschr., 1931, lxxviii, 1639-1642.
37. ASCHOFF, L.: Die Erkrankungen der steinfreien Gallenwege. Anatomisches Referat, Verhandl. d. deutsch. Gesellsch. f. inn. Med., 1932, xlv, 261-289.
38. HIYEDA, K.: Experimentelle Studien über den Ikterus: Ein Beitrag zur Pathogenese des Stauungsikterus, Beitr. z. path. Anat. u. z. allg. Path., 1925, lxxiii, 541-565.
39. SAUNDERS, W.: A treatise on the structure, economy, and diseases of the liver; together with an inquiry into the properties and component parts of the bile and biliary concretions, 1797, W. Pelham, Boston, p. 78.
40. BLOOM, W.: The rôle of the lymphatics in the absorption of bile pigment from the liver in early obstructive jaundice, Bull. Johns Hopkins Hosp., 1923, xxxiv, 316-320.
41. EPPINGER, H.: Beiträge zur normalen und pathologischen Histologie der menschlichen Gallencapillaren mit besonderer Berücksichtigung der Pathogenese des Ikterus (auf Grund einer neuen Färbungsmethode), Beitr. z. path. Anat. u. z. allg. Path., 1902, xxxi, 230.
42. SHAFIROFF, B. G. P., DONBILET, H., and RUGGIERO, W.: Bilirubin resorption in obstructive jaundice, Proc. Soc. Exper. Biol. and Med., 1939, xlii, 203-205.
43. MINKOWSKI, O.: Zur Pathogenese des Icterus, Ztschr. f. klin. Med., 1904, lv, 34-43.
44. NAUNYN, B.: Cited by H. Eppinger.⁵
45. PICK, E.: Ueber die Entstehung von Icterus, Wien. klin. Wchnschr., 1894, vii, 478-479.
46. UMBER, F.: Erkrankungen der Leber, der Gallenwege und der Pankreas, Handbuch der inneren Medizin, Bd. III; Teil 2, 1926, J. Springer, Berlin, pages 22, 92.
47. URTEAGA, O.: Algunas Observaciones en el Campo de la Fisiologia Fisiopatologia y de la Anatomia Patologica del Hígado in Relacion con el Problema de la Ictericia, Separata Publicado en la Revista de Anales de la Facultad de Ciencias Medicus, 1943, Tomo xxvi, Lima, 258-287.
48. AXENFELD, H., and BRASS, K.: Klinische und bioptische Untersuchungen über den sogenannten Ikterus catarrhalis, Frankf. Ztschr. f. Path., 1942, lvii, 147-236.
49. LUCKÉ, B.: The pathology of fatal epidemic hepatitis, Am. Jr. Path., 1944, xx, 471-595.
50. JONES, C. M., and MINOT, G. R.: Infectious (catarrhal) jaundice. An attempt to establish a clinical entity, Boston Med. and Surg. Jr., 1923, clxxxix, 531-551.
51. BLOOMFIELD, A. L.: The natural history of chronic hepatitis (cirrhosis of the liver), Am. Jr. Med. Sci., 1938, cxcv, 429-444.
52. MALLORY, F. B.: Cirrhosis of the liver, New England Jr. Med., 1923, ccvi, 1231-1239.
53. KARSNER, H. T.: Morphology and pathogenesis of hepatic cirrhosis, Am. Jr. Clin. Path., 1943, xiii, 569-606.
54. BERGSTRAND, H.: Ueber der akute und chronische gelbe Leberatrophie. Mit besonderer Berücksichtigung ihres epidemischen Auftretens in Schweden im Jahre 1927, 1930, Georg Thieme, Leipzig.
55. LUCKÉ, B.: The structure of the liver after recovery from epidemic hepatitis, Am. Jr. Path., 1944, xx, 595-620.
56. HANOT, V.: Des différentes formes de cirrhose du foie, Arch. gén. Méd., 1877, tome 30, VI e série, ii, 444-469.
57. KLEMPERER, P.: Chronic intrahepatic obliterating cholangitis, Jr. Mt. Sinai Hosp., New York, 1937, iv, 279-291.
58. RÖSSLE, R.: Entzündung der Leber, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, 1930, Berlin, Julius Springer, Bd. v, Teil 1, 338.

59. PATEK, A. J., JR., and POST, J.: Treatment of cirrhosis of the liver by a nutritious diet and supplements rich in vitamin B complex, *Jr. Clin. Invest.*, 1941, xx, 481-505.
60. WEBER, F. P.: On biliary cirrhosis of the liver, with and without cholelithiasis, *Trans. Path. Soc., London*, 1902, liv, 103-135.
61. HOFFBAUER, F. W., EVANS, G. T., and WATSON, C. J.: Cirrhosis of the liver presenting the clinical features of xanthomatous biliary cirrhosis, but without confirmation at autopsy, *Med. Clin. N. Am.*, 1945, 1054-1055.
62. HALLOCK, PHILLIP, and HEAD, D. P.: Simple laboratory test as an aid in recognizing early hepatitis, *Bull. U. S. Army Med. Dept.*, 1946, v, 236-242.
63. WATSON, C. J.: Some newer concepts of hemoglobin derivatives and related compounds. II. The serum bilirubin and bilirubinuria, *Blood*, 1946, i, 99-120.
64. KRARUP, N. B., and ROHOLM, K.: Development of cirrhosis of liver after acute hepatitis, elucidated by aspiration biopsy, *Acta med. Scandinav.*, 1941; cviii, 306-331.

MEDICINE AND EDUCATION *

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EDUCATION has been described as the "taking on of the arts and sciences and of moral attitudes which make up the fabric of civilization." In this process, educated people acquire an appreciation of values, the ability to think and to see the relations of the values to each other in human living. Unfortunately, as George Vincent put it, many people do not think; they merely rearrange their prejudices. The Harvard report well states the general problem. "The aim of education should be to prepare an individual to become an expert both in some particular vocation or art and in the general art of the free man and citizen. Thus the two kinds of education once given separately to different social classes must be given to all alike." "The aim of general education may be defined as that of providing the broad critical sense by which to recognize competence in any field." The observation of Henry Morrison that "We do not learn what to do, but rather become the kind of people who will know what to do," is well exemplified in the varying quality of performance of interns in our hospitals.

In medicine defects in education become evident, when we analyze the quality and performance of the graduates of medical schools. I speak now of the mentally well endowed students, ambitious, hard working, who nevertheless fail to prosper as well as they might, because of an evident lack of training to think, and to set down their thoughts in good English. This inferiority, or perhaps one should say more politely, this lack of completeness in premedical education in a number of respects that go to make up the somewhat nebulous term "culture," has been accentuated by the recent acceleration of medical education made necessary by the needs of the armed services. But it had been increasingly evident in the decades preceding the present war.

War is always wasteful and its serious effects on education in general are clearly evident in the field of medicine. Besides the distraction and disturbance of general thinking, medicine has suffered through the abbreviation of premedical preparation, the acceleration of the medical course with its condensation of four years into three; the concentration of the internship, and the elimination of residencies for two thirds of the young physicians under the formula that allotted nine months each to internship, assistant residency and residency. To those of us who were brought face to face with the medical emergency of the armed forces, the acceleration of the medical educational program seemed a necessary and therefore a desirable compromise, to which we subscribed as a wartime measure. This acquiescence, in keeping with the evident needs of the hour, did not mean that we were unaware that educational standards were being sacrificed to immediate necessity by these pro-

* Presidential Address, Victory Convocation, Twenty-Seventh Annual Session, American College of Physicians, Philadelphia, May 15, 1946.

cedures. The speeding up of the curriculum with shortening of some courses and the introduction of others, no doubt eliminated some time-honored, but unnecessary courses, which up to then, entrenched behind ramparts of custom and personal interest, had withstood previous efforts to remove them. But against this relatively slight gain must be assessed the hurry and tendency to superficiality of a rapidly moving program, and the impossibility of exploring adequately the by-paths of educational interest. In his hurried acquisition of prescribed facts, the student lacked the time as well as the strength for collateral reading; his jaded mind failed to respond to such impulses of curiosity as he might fortunately experience. The superior students felt this keenly; the weaker students never knew what they missed.

Later in the war program, those in military authority were given unfortunate advice regarding education which led to the reduction of the supply of properly trained candidates for medical schools. The serious results of this mistaken policy will be felt by the public for years to come. Nursing education has suffered in much the same way as has medical education.

Perhaps a physician is presumptuous in discussing problems of general education in regard to which professional educators are vigorously battling among themselves, seemingly unable to agree. Nevertheless, most of the faults that educators of the several camps point out, are clearly evident in results of our attempted education of physicians. We lament the lessening knowledge of the classics, the limitation of sources of knowledge by lack of even superficial facility not only in Greek and Latin, but in modern languages such as French, German and Spanish.

The tremendous advances in science in this country have indeed overshadowed the influence of the classics. But this imbalance exists throughout general education also, and is attributable to the expansion of the educational system, changes in society, and to what has been described as the "headlong growth of knowledge." Classicism flourished when but little was being done to remedy the ills of poverty and low standards of living. Then came science and mechanical arts which raised standards of living so that the deficiencies of previous centuries under classicism became evident. Today, neither classicism nor science can march alone.

In medicine the balance can be restored in part at least by the assumption of an increased leisure, or perhaps better a deliberateness and thoroughness which will decrease the unreasonably rapid tempo of preparation for medical and scientific education. By insistence on a more thorough ground work in the classics, languages and history, the student will acquire tools and a cultural point of view that will serve him well as a responsible citizen in a democracy and in his educational life which has only begun when he leaves the portals of college and medical school. The cultural background should be broad, and the tools of good quality.

Not all people, even some of the intelligent, are interested in the thought-mechanisms of the ancients, as presented in the 100 books recommended by some educational leaders as necessary to education. But there is much sound

advice, as well as a certain pathos in the voices of the classicists, small in number but vociferous, crying aloud in a wilderness of science.

Before accepting at face value the charges of one group of educators that an opposing group is "authoritarian" or that another is "practical" or "vocational" and therefore lacks intellectual ideals, it might be profitable, even at the risk of seeming repetitive and perhaps "undemocratic," to consider the purposes to which the recipients of education plan to devote what they learn. For, unpleasant as it may be to those who would insist that we are born "free and equal," the fact remains that we vary greatly in our mental and physical endowments as well as in our acquired ambitions. Not all people in like positions are of like productive ability. Some, more than others, are able from the beginning to assimilate cultural elements; some seem incapable of being educated.

In medicine there is an ever increasing need for scholarly attainment not alone in the scientific fields so that the physician may understand the language and utilize the discoveries of the lightning-like advances of science, but in cultural and historical fields so that he may evaluate properly the medical, social and political changes about him. He should begin as early as possible to prepare himself for intellectual leadership.

But in medicine and I suspect in other educational groups the difficulty goes even deeper. Many candidates for admission to medical schools lack facility in reading, writing and spelling and consequently in ability to acquire and express ideas. They do not know the rudiments of English grammar. This in turn reverts to slovenly training in the secondary grades. One wonders how many of their teachers know the fundamentals of English grammar. And in those schools of supposedly better heritage in which education is called progressive, the slogan of making education pleasant and non-competitive negatives in practice the acquirement of precise knowledge and exact attainment. The contention that "usage" should be the supreme guide to the acquirement of good English overlooks the fact that usage is concerned with the choice of words to express ideas and cannot replace correct spelling and grammar, which are based on formal conventions. Possibly while the youngster is being taught to think, he might be induced to learn to add, subtract and spell.

The apparent deterioration in quality of modern secondary education, while perhaps due in part to unwise emphasis on the joy of making education pleasant for the child, is not to be charged to sabotage of standards, or perverseness, or original sin. Gideonse has emphasized what has been repeatedly pointed out, that a chief cause of educational ineffectiveness is related to the rapid extension of education downward. It is a defect not peculiarly American, but according to reports is a recognized problem in English, Dutch, French and Russian education. This expansion of education downward to large masses of people previously scarcely educated at all, necessarily involves dilution of effort, and makes necessary the inclusion in the teaching group of a number who themselves are not up to previous stand-

ards. Reduction of standards of quality of goods or of services results in reduction of standards of living, in this case reduction in standards of education. This is especially true in large cities, many of whose school systems obviously have outgrown their physical facilities, and perhaps less evidently, but just as fatally, their teaching force. In rural communities the problem presents what the Director of Education, Mr. Studebaker, has called the "inefficiency of smallness." This is being remedied by the establishment of regional and township high schools. The little red school house still serves well, but its scope is limited, and needs to be supplemented by a larger and more advanced unit.

The repair of defects in secondary and general education will require time and vast effort. Even after entrance to the decelerated medical course, students as now educated may be introduced to collateral lines of reading, such as medical history, which itself inevitably will necessitate some exposure to political and economic history. The correction of other fundamental faults in the preparation for the medical as well as for other professions awaits also the elimination of the frequently wasted two years in the primary grades and the replacement of mere college credits by real educational values. Such a general education should provide a broad cultural basis in the humanities as well as in science, a change which will afford untold satisfactions in later life.

Within the structure of the medical curriculum itself, there have developed over the years stresses and strains between preclinical and clinical departments, again largely ascribable to the rapid increase in knowledge, which has forced specialization in the basic and preclinical medical subjects, just as in the clinical. There have resulted educational fissures and gaps; sometimes major quakes have further separated basic from clinical medicine. These faults are being slowly eliminated through the attainment of a better understanding of the problems of each group by the other.

It may be urged that the physician is now 26 or 27 years old when he enters the practice of medicine, that his preliminary and medical education has already been improved by the creation of the combined college-medical course of six or seven years, that the need for physicians demands an increase rather than a decrease in output, and that increased training adds indirectly to the cost of medical care. All this is admitted. But relative economic and educational values need to be considered. Some years ago when the evident educational deficiencies of medicine were beginning to be remedied, a proposal was suddenly made to reduce standards of medical education, so that there would be more doctors available to go to understaffed and neglected areas especially in the South. This proposal, by men sincere, but of limited vision, failed to consider that the medical plight of these areas was only symptomatic of bad fundamental economic conditions, that reduced standards of training would reduce quality of performance, and that men willing to accept such inferior training would lack also the idealism necessary to sustain them in situations of increased difficulty. Fortunately the economic origin

of this distress was recognized before the destruction of standards of medical education had been accomplished.

Some 10 years ago the Commonwealth Fund undertook to provide education for men in medicine under an agreement that they would settle in backward and poorly staffed communities. In practice it was found, however, that many of these men tended to avoid the very districts where they were most needed and that some failed to keep the agreement at all. Without condoning the breaking of agreements it may be observed that in the absence of suitable economic and hospital facilities one could hardly expect progressive young doctors to resign themselves to making bricks without straw. In spite of chimerical arguments of recent years that somehow economic laws have changed, the laws of supply and demand, of human nature, and of opportunity, remain the same as in previous centuries in education as in business.

EDUCATION AND MEDICAL RESEARCH

The bounding progress of scientific knowledge, to which medicine owes much of its own astonishing accomplishments in the amelioration of suffering and the saving of lives, has come through the free mental activity of men trained to think rationally and at the same time to give free rein to their imaginations. While entirely new concepts occasionally necessitate an extensive rearrangement of previously held notions, in the main the progress of today rests on the labor of yesterday.

The man who proposes to engage in research requires first a broad general education in order that he may develop an unconscious critical sense, the first line of defense against wild and unworkable theories. Some men never acquire this discriminative ability nor have they the diligence to learn what has already been done, and they fall victims to, and sometimes become protagonists of procedures which in the end do harm to the cause of medical science. Some even deserve the cynical comment of a celebrated wit: "If you steal from one author, it's plagiarism; if you steal from many, it's research." Manifestly this remark is unfair to good research. It does, however, characterize certain reports which masquerade under the name of research. Inquiry usually will disclose gaps in the early education of such authors.

The benefits of fundamental research, the result of private expenditure of some thousands of dollars, have been so overwhelmingly demonstrated in the war now ending, that research is confronted with a new problem, that of withstanding popularity. It is assumed that since the value of research to the nation has been so outstanding, more research will be still better and the government should invest millions against the previous privately supplied thousands, and go in for the purchase of research in a big way. Varying opinions are held as to the advisability of government subsidized research; some hold that government funds are needed to reinforce private sources now being exhausted by heavy tax burdens; others maintain that the entry

of government funds into the research field will itself discourage the further contribution of private sources.

But more important than these questions is that of the method of utilization of these funds. Imagination and ideas cannot be grown to order; they come from unsuspected places. After the initial idea or concept is born, collateral lines of approach must be explored patiently and often without tangible result. The scientific method cannot be forced. And so research must be free—free from the demands of today or tomorrow. Such freedom is best realized in universities; workers must be under no compulsion other than the inner driving force of their genius. If government funds are to be used to advantage, they should be under the direction of universities which have already demonstrated their ability to utilize to advantage their own funds free from any governmental obligation or political interference.

EDUCATION IN RELATION TO STATISTICS AND PROPAGANDA

Physicians share with other citizens the necessity of education in the interpretation of statistics. It is easy to state only a part of the truth. Recently the statement appeared, quoting from an authoritative article on nutrition: "Only one American in a thousand is really well fed." One is led to conclude that Americans as a whole are existing on a marginal diet. The complete sentence reads "Only one American in a thousand is really well fed, in the sense that no further improvement in his physical condition could be made by changes in his diet." While one might challenge the general application of this latter statement, it is clear that the use alone of the first portion of the sentence is an attempt to influence public opinion by disseminating an untruth.

It is claimed that an alarming percentage of school children fail to meet ideal figures of height or weight. Should a couple of pounds over or under the average standard or a cavity in one tooth consign an otherwise healthy child to the category of an imperfect and therefore defective class?

The same kind of misinterpretations of draft statistics has given the impression to the uninformed that the American nation physically is about to fall to pieces. We have been told that the 4,000,000 rejections of draftees indicate a frightful state of medical decrepitude, which requires an immediate rearrangement of all medical service. The facts are that only a fraction of these rejections were for remediable medical defects. By a sane program many defects can no doubt be prevented or remedied, but illiteracy and feeble-mindedness can hardly be cured by any system of medicine. The fallacies involved in assuming that the 4,000,000 draft rejections are a fair index of the nation's health are further emphasized by the recent willingness of the army, which even now must have able bodied men, to enlist thousands of these same men who were previously rejected.

Still other misquotations and misuse of statistics are made in discussions of statistics of morbidity and mortality. League of Nations' statistics are

used without discrimination as to conditions existing in countries under discussion. The manufacture of misleading data out of incompletely digested statistics seems to be a too common practice in some governmental circles.

In this country in support of a highly desirable nationwide campaign against venereal disease, figures on the incidence of syphilis among poor negro populations in backward counties in the South were quoted as if the same conditions were present in the north central states. The excuse given was that people must be shocked into action.

SPECIAL BOARDS

The widening scope of medical knowledge, in addition to requiring vastly more information and preparation of the modern doctor, has made it necessary for some to devote still more time and effort in perfecting themselves in special departments; therefore special fields developed and more recently special examining boards to determine minimal standards of performance in these specialties. The operation of the several boards of medical specialties designed primarily for the protection of the public, has resulted in an amazing and unanticipated stimulation of thousands of young doctors to spend at least five additional years in preparation in their chosen specialties. Whether or not they finally pass the boards, the quality of their current and subsequent service to the public is greatly enhanced, and a further improvement of medical public service results. A broad educational foundation will assist the young physician to appraise the value in medical practice of the many new methods and instruments designed to contribute to accuracy and completeness of diagnosis. Some of these, like some drugs, will be found valuable; others will be determined inaccurate or misleading. The acquirement of clinical sense and experience will help the physician to use such apparatus intelligently where needed, and to avoid their use as occupational gadgets.

The special boards, unlike boards of state licensure, have no legal status, and the participation of any doctor is entirely voluntary. The wide acceptance of standards set by special boards often has led organizations and hospitals charged with the selection of staffs to require certification by a special board as a prerequisite for appointment. With such appointments, the boards have nothing to do; they have only set certain standards, for certification, of which any organization may avail itself. No doubt there are many men of equal ability and experience who have not cared to apply for certification or submit to examination. The educational requirements preliminary to admission to examination are suggested by the boards for the protection of the candidates, so that they shall not spend five or more years in inferior training only to find later when the golden period of opportunity of youth has passed, that they have failed. Here, too, it is tragic to observe the occasional young doctor who comes for his examination before special boards with a reasonable preparation of theory and factual information, full

of ambition; idealism and often imagination, but hampered by an evidently faulty secondary and premedical education and unable adequately to express his ideas in intelligible and decipherable English.

Some concern has been expressed over the great increase in physicians who are taking board examinations because it is feared that soon there may be too many specialists. Here again, it would seem that we may safely depend on the law of supply and demand. Certainly the desire to acquire additional preparation and facility in a branch of medicine is to be encouraged, rather than condemned; the public will gain in better quality of service. There is, however, complaint from many patients, that the young doctor having passed his board, now feels that he is relieved of all obligation to care for his patients in their homes when they are unable to come to him. While the younger physician must conserve his time and strength if he is to continue to grow in medicine, he should not forget that the greatest gratification in the practice of medicine is the close patient-physician relationship of the family doctor. He will do well not to allow a false estimate of his own dignity, nor too much solicitude for his own convenience, or for financial gain, to rob him of this jewel among the rewards of medicine. He should not assume that by improving his qualifications for the practice of medicine, he has disqualified himself as family advisor and friend. His experience will be greatly enriched by his observation of even minor illnesses in the home. The better prepared physician of the future will still retain the ideals of medicine; the family doctor will not have passed—he will have improved.

Medical problems of the future, including prosecution of medical research foretold the necessity of even more educational preparation than is needed to meet the problems of our day. Some familiarity with the events and thinking of the past will help the physician to understand the significance of current social, economic and political changes. A knowledge of history will contribute to tolerance, and at the same time will tend to prevent errors of judgment incident to emotional thinking. A good general education is necessary to the physician of the future, so that with its aid, he may excel in his profession, and still more important, he may take a worthy place in the citizenship of a democracy in a free society.

INFECTIOUS MONONUCLEOSIS: REPORT OF AN EPIDEMIC IN AN ARMY POST *

Part II

By HARRY F. WECHSLER, Lt. Col., ARTHUR H. ROSENBLUM, Capt.,
and CHARLES T. SILLS, Capt.

11. *The Cardiovascular System.* Our knowledge of the possible effects of infectious mononucleosis on the heart is extremely meager. The literature on this subject is summarized, but not critically analyzed, by Bernstein.⁵⁰ He, however, states that "despite the scantiness of these bits of evidence, one wonders whether certain of the so-called rheumatic hearts encountered in individuals with no history of rheumatic fever or its equivalents, may not date back to a seizure of infectious mononucleosis."

In 1914, two English physicians, Pruen⁵⁰ and Kirkland,⁵¹ under the title of "Epidemic Cervical Adenitis with Cardiac Complications," reported their observations on a large number of cases which they had seen in 1912. The former observer had 14 cases with cardiac complications out of a total of 60, while the latter had 10 per cent of myocardial or endocardial involvement in several hundred cases. The disease they describe has little resemblance to infectious mononucleosis and no blood counts were taken. Indeed, the authors themselves did not believe they were dealing with infectious mononucleosis but with a streptococcus infection. Smears of the throats showed streptococci and blood culture in several cases grew the same organism.

Longcope,³⁵ in 1922, reported 10 cases of infectious mononucleosis, two of whom had premature contractions. The first case, a woman of 30, can be dismissed, as no further observations were made. The second, however, is more interesting. An Italian girl of 12, following a tonsillectomy 19 days before admission, had intermittent fever, malaise, constipation and occasional vomiting. Five days before admission, she developed a red, macular, generalized rash and abdominal pains, which were at times confined to the right side. She had had frequent attacks of tonsillitis previously, and six months before admission she had had pains in the right shoulder without fever for one month. Physical examination showed a macular rash on the abdomen, slight injection of the throat, enlarged submaxillary, axillary and inguinal nodes, small but tender posterior cervical nodes, a soft systolic murmur at the apex, some accentuation of the pulmonic second sound and premature contractions. The blood count was characteristic of infectious mononucleosis with the exception of the red blood cell count. In the space of three days, there was a drop in the red count from 7,140,000 to 3,800,000

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Major Jesse Schapiro supervised the laboratory procedures. Major Louis Johnson assisted in the preparation of the dermatologic section.

For Part I of this article see the preceding issue of this journal.

and in the hemoglobin from 80 per cent to 68 per cent. Such a drop does not occur in infectious mononucleosis without the presence of a complication and one must, therefore, either doubt the correctness of the diagnosis or conclude that the infectious mononucleosis was complicating some other illness such as rheumatic fever. An electrocardiogram is reported in this case as showing a P-R interval of 0.14 to 0.16 sec., ventricular premature contractions and an inverted T-wave. As no lead is mentioned, the significance of the inverted T-wave must remain in doubt.

In 1930 Du Bois⁵² reported the case of a 26 year old male with infectious mononucleosis who developed an extensive empyema of the right pleural cavity. At autopsy, a rheumatic-like vegetation was found on the mitral valve. Although the pleural fluid was said to be sterile, it is highly probable that the empyema was due to a secondary infection and could also have been the cause of the endocarditis.

Finally, Bradshaw,⁵³ in 1931, reported the case of a young girl of 17, who was known to have had a normal heart previously and who, as rapidly as six weeks after the recovery from an attack of infectious mononucleosis, was found to have definite evidence of mitral stenosis. The clinical description and the blood counts could very well fit a case of infectious mononucleosis with jaundice, except that the author states that only rarely was a morphologically abnormal lymphocyte found. The rapidity with which evidence of mitral stenosis was discovered after her illness and the persistence and rapid progression of the lesion would favor the view that the murmur had been present prior to her attack of infectious mononucleosis rather than secondary to an acute valvulitis. It is well known that the murmur of mitral stenosis is frequently difficult to hear or is even inaudible at times.

Our attention was directed to the heart in infectious mononucleosis by the unexpected discovery of a markedly prolonged P-R interval in an otherwise typical case. This case will be described in detail.

CASE REPORT

A negro soldier, aged 29, was admitted on September 7, 1943, with the complaints of sore throat, chills, fever, headache, nausea, vomiting and pains in the epigastrium. These symptoms began abruptly the day previously. He had malaria in 1933, with no recurrence since. In 1941, he was treated for "low blood pressure" because of dizziness. He had been admitted to this hospital on May 17, 1943, for a non-specific urethral discharge. During his stay, he complained of epigastric pains, bloating and belching. A gastrointestinal series and gall-bladder roentgen-rays were negative. A gastric analysis revealed a low acidity. He was discharged to duty on July 2, 1943.

On admission, his temperature was 103° F. and his pulse rate 94. Physical examination revealed a well-developed and well-nourished male adult, who looked acutely ill. The pharynx and tonsils were injected. There was a moderate generalized lymphadenopathy. The spleen was palpable one finger's-breadth below the costal arch. The rest of the examination was essentially negative.

The blood count on admission was: white blood cells 10,700; neutrophils 89 per cent, lymphocytes 10, eosinophiles 1. Serial blood counts revealed a progressive decrease in his total white blood cell count and a rising mononucleosis. Large num-

bers of "leukocytoid" lymphocytes were present. The white blood cell count on October 6, 1943 was: white blood cells 5,900; neutrophils 33, lymphocytes 67. The heterophile antibody agglutination titer on September 10 was 1:56 and on October 6, 1:448.

He had a fever for but two days and remained afebrile thereafter. On September 11, four days after admission, he complained of sharp precordial pains. Because of a heart rate of 44 and a marked sinus arrhythmia, an electrocardiogram was taken. It showed a P-R interval of 0.24 sec. and a rate of 40.

He continued to complain of occasional precordial pains. The bradycardia persisted. A faint soft systolic murmur was audible over the apex. Serial electrocardiograms (figure 6) showed an increasing degree of heart block. On November 6, the P-R interval was 0.44 sec. In December and the early part of January (figure 7), a second degree heart block was present, usually with a 7:4 ratio. Thereafter, the P-R interval varied between 0.36 sec. and 0.42 sec.

The erythrocyte sedimentation rate, which was 29 mm. in one hour on admission, rose to 56 mm. a week later and then remained within normal limits, except for a reading of 25 mm. on November 22 and of 35 mm. on December 3. The blood Kahn test was negative. No sickling was present. Bacterial agglutination titers were: *E. typhosa* 1:80; Para A and B, negative; *B. abortus*, negative; *Proteus* OX-19, negative. Throat cultures for *Streptococcus hemolyticus* were negative. An anti-fibrinolytic titer, performed four months after the onset of his illness was 2 plus and then gradually became negative. Roentgen-rays of the chest showed a moderate increase in the size of his heart by November.

After the first few weeks he had no complaints. A diastolic murmur was never audible. The bradycardia, systolic murmur, moderate enlargement of the cardiac shadow and a normal sedimentation rate were present on his discharge, eight months after the onset of his illness.

Because of this striking and unusual case, electrocardiograms were taken of 223 patients in this series. Excluding deviations of the S-T segments, low voltage and minor slurring of the QRS complexes, 53 patients had abnormal electrocardiograms, 23 per cent of the group. These patients were closely observed, and the analysis of our findings is summarized.

Previous History: There were six patients with a past history suggestive of rheumatic fever. Three of these had suffered from a definite polyarthritis, one had scarlet fever at the age of five and pains in the knees at the age of 13, one had vague rheumatic pains in the legs between the ages of seven and 12, and the last had an attack of swelling and weakness of the right knee, unaccompanied by fever, four or five years prior to admission. One patient, without a history of rheumatic fever, had been found to have a heart murmur three years previously.

Clinical Course: In general, there was little to differentiate this group from those with normal electrocardiograms. Those patients with acute onset and febrile course were more severely ill, and their temperatures tended to reach a higher peak. There were 49 per cent of this group with temperatures of 102° F. and over, as against 32 per cent for the series as a whole. On the other hand, there were 13 cases who were afebrile during their hospital stay. There was a greater tendency toward relapses of the infectious mononucleosis, eight of the group suffering such a relapse. There were no cardiac symptoms, except for an occasional patient who complained of inter-

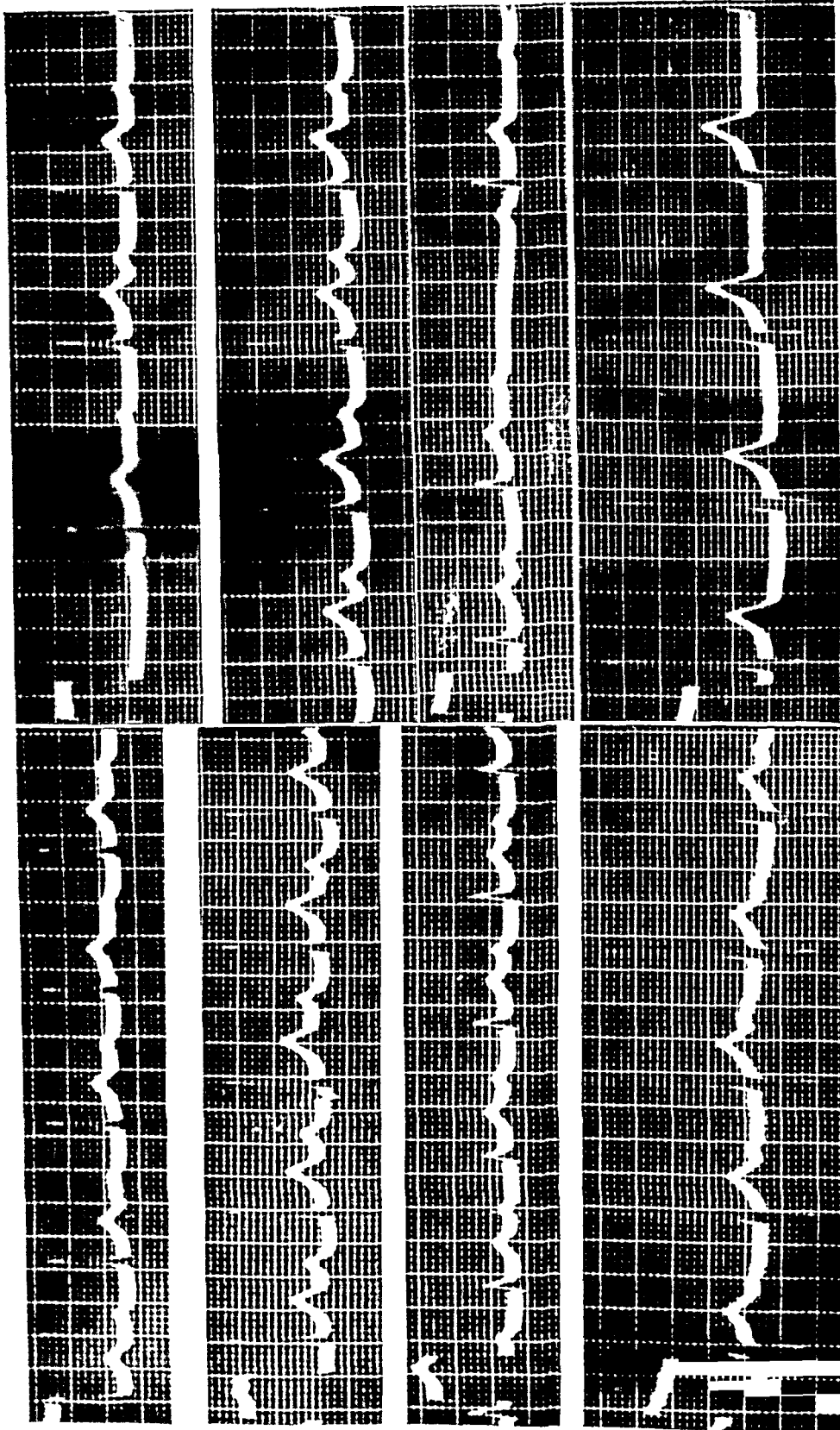


FIG. 6.

FIG. 6. Electrocardiogram taken Oct. 11, 1943. The rate is 75 and the P-R interval 0.32 sec. There is a blocked auricular premature systole in Lead II.

FIG. 7. Electrocardiogram taken Jan. 3, 1944. The rate is 60 and the P-R interval 0.40 sec. A ventricular complex is dropped in Lead III and is followed by a normal P-R interval.

FIG. 7.

mittent sharp precordial pains. The other manifestations of the disease were as varied as for the series as a whole. There were two patients with pneumonia, one of whom showed a polymorphous type of eruption in addition. Six others of the group had eruptions, three scarlatiniform, two morbilliform and one maculopapular. There were two patients with jaundice and one with nephritis.

Cardiac Findings: Abnormal physical findings relative to the heart were scanty. Cardiac enlargement was demonstrable in only three of the cases. In one there was a history of a "murmur discovered three years previously." A presystolic murmur was audible, and on roentgen-ray the left auricle was prominent, the left ventricle was slightly enlarged, and the cardiac shadow was 12.5 per cent above the predictable size for his height and weight. A patient with a persistent hypertension showed slight enlargement of the left ventricle. The only case in which there was no evident cause for cardiac enlargement was the one described in detail above. The enlargement was 22 per cent above the predictable size.

A faint systolic murmur was audible over the precordium in 22 cases. It was usually loudest over the apex and of short duration. It varied in intensity with exercise and position and was heard best in the left lateral position.

Premature contractions were noted in five cases, in one of whom they were definitely known to have been present prior to the onset of the present illness.

A bradycardia and sinus arrhythmia were practically always present after the fever had subsided. They persisted as long as the abnormal electrocardiographic changes were demonstrable and occasionally for a longer period.

Laboratory Data: The blood counts, the percentage of "leukocytoid" lymphocytes and the heterophile antibody agglutination titer were not significantly different from those in the other cases in this series. Repeated erythrocyte sedimentation rates showed an increased rate at the onset in those with acute manifestations of the disease. The range was between 20 mm. and 66 mm. in one hour. After the temperature returned to normal and in the insidious cases the sedimentation rate was within normal limits and remained so in the great majority in spite of varying electrocardiographic findings. In a few of the cases who were observed for many months, there were occasional slight irregular rises in the sedimentation rate. The blood Kahn test was negative in all. Throat cultures were performed in 28 of the group and 13 were positive for *Streptococcus hemolyticus*. Through the courtesy of Dr. William S. Tillett, who furnished us with a strain of hemolytic streptococcus known to be highly active in the production of fibrinolytic substances, serial anti-fibrinolysin titers were performed in 23 cases according to his method.⁵⁴ Unfortunately, anti-streptolysin titers could not be done. In 16 of these there was unmistakable evidence of the presence of anti-fibrinolysins in the circulating blood. One plus reactions, present in six cases, were disregarded.

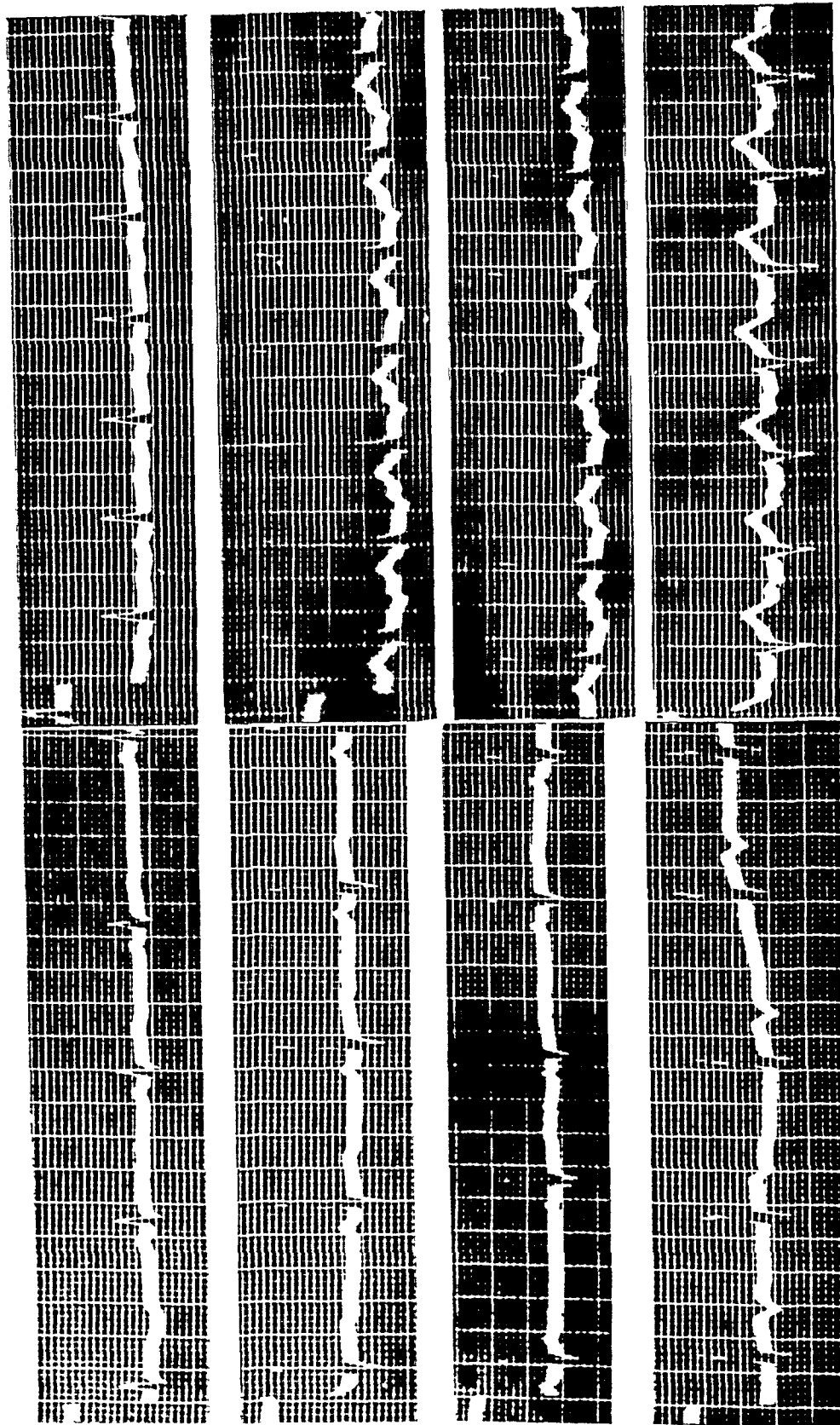


FIG. 9.

FIG. 8.

FIG. 8. Isoelectric T₁; low voltage T₂; T₃ upright; T₄ inverted.

FIG. 9. Low voltage T₁; T₂ and T₃ inverted.

Only one case was completely negative on repeated examinations. The anti-fibrinolysin titer usually reached its height in three to four weeks and then gradually decreased. The maximum titer was 4 plus in 11; 3 plus in 2; and 2 plus in 3. Positive throat cultures for *Streptococcus hemolyticus* were not always found in those cases with a rising anti-fibrinolysin titer.

Electrocardiograms: An electrocardiogram was taken within a few days after hospitalization. Routinely, the tracings consisted of the three standard limb leads and the apical chest lead, all taken in the recumbent position. Serial tracings, usually at five day intervals, were made in all who exhibited any deviation from the normal and in many whose initial electrocardiogram was normal. Abnormalities of the T-waves did not develop in any case subsequently, if they had not been present on the initial tracings. This was not true of the prolonged P-R intervals, although the majority followed this rule. There were records of electrocardiograms taken during a previous hospitalization in only two of the abnormal group and in both of these they were normal. The 53 patients with abnormal electrocardiograms could be conveniently divided into three groups: Abnormal T-waves, 39; prolonged P-R interval, 8; prolonged P-R interval and abnormal T-waves, 6. Changes in the voltage of the QRS complexes or in the S-T segments were not considered as of significance and were not listed as definitely abnormal.

The T-waves were either abnormally low, isoelectric or inverted (figures 8 and 9). When involved, the T-waves in all leads were affected but not to the same degree. T_1 showed the greatest change in all but three. In the latter, T_2 showed the greatest depression. In 13 cases with abnormality of T_1 , the other T-waves were not abnormal but increased in amplitude as T_1 improved in voltage. Ten of the group were discharged from the hospital as soon as their tracings returned to normal. The remaining 29 were observed for longer periods and all exhibited a peculiar waxing and waning of the T-waves (figures 10 and 11). These repeatedly became taller or upright, and at times reached 1 mm. in amplitude but then reverted to their original appearance. Many of these cases were under observation for as long as six months without essential change in this cycle. It is possible that the 10 patients who were discharged soon after their tracings were found to be normal, might also have exhibited this phenomenon if further tracings had been taken. The abnormal T-waves were not appreciably affected by changes in position, respiration or large doses of belladonna.

The 14 exhibiting a prolongation of the P-R interval (figure 12), with or without associated T-wave changes, can be considered together as the behavior of the abnormal T-waves did not differ from that already described. Included in the group are two patients whose P-R interval increased from 0.16 sec. to 0.20 sec. without a change in the heart rate and which, a week later, returned to 0.16 sec. In the remaining 12 cases, the P-R interval ranged between 0.22 sec. and 0.40 sec. Second degree heart block occurred temporarily in two. The interval varied considerably during the period of observation and was unaffected by exercise or belladonna. Besides the two

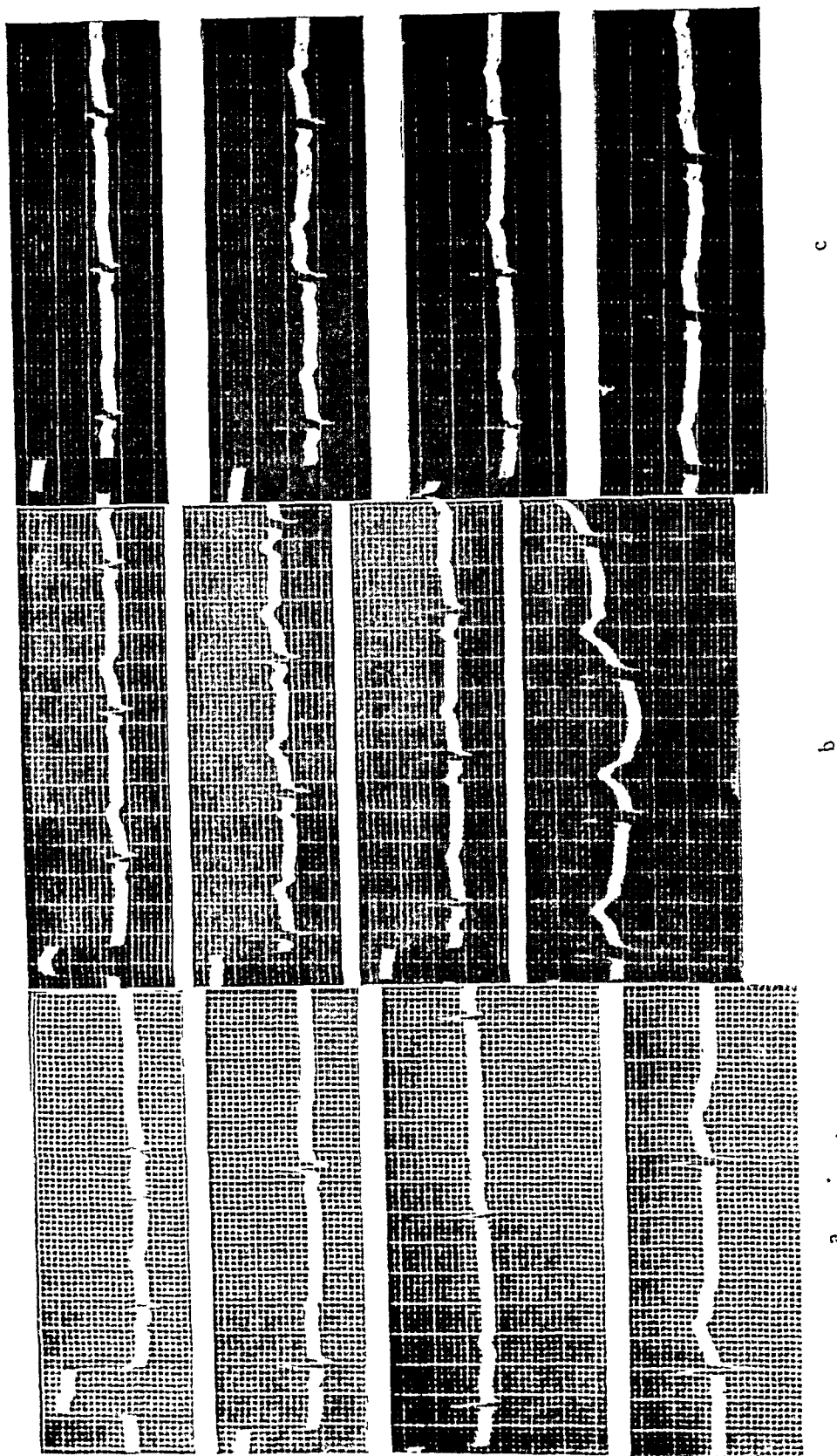


FIG. 10. (a) Isoelectric T_1 and low amplitude of T_2 .
 (b) The same patient, five weeks later. Improvement in voltage of all T-waves. T_1 and T_2 are now within normal limits.
 (c) The same patient, nine days later. T_1 is again markedly reduced in amplitude.

cases mentioned above, the P-R interval became normal in five additional patients in from 28 to 55 days, with an average of 40 days. In the remaining seven cases, a prolonged P-R interval was still present on discharge, four to nine months after the onset of their illness. The T-waves exhibited the same waxing and waning as previously described for the first group. They were within normal limits on discharge in four and persistent in two.

There were many other findings in the electrocardiograms which were considered to be either not definitely abnormal or preëxistent. There were many with low voltage of the QRS complexes. Five showed abnormal depressions of the S-T segments; one in all three leads and the others in S-T₂ and S-T₃. There were eight cases with premature contractions, five auricular in origin. Three of these were unassociated with other abnormalities and were not considered as significant. There were two cases of nodal rhythm which reverted to normal sinus rhythm during convalescence. One patient exhibited a short P-R interval and a prolonged QRS. He had a marked funnel breast, and there was no history of paroxysmal tachycardia. One patient, with the findings of an old mitral stenosis, showed a right ventricular preponderance.

The interpretation and the significance of the cardiac findings in this epidemic require critical evaluation. It does not seem likely that they were merely coincidental, in view of the large percentage of patients affected, the normal electrocardiograms in two of the patients prior to the onset of their illness and the appearance of prolonged P-R intervals during the course of the disease. These facts, however, do not eliminate the possibility of the co-existence of two independent diseases, especially the possibility that infectious mononucleosis was complicating rheumatic fever.

Although it is manifestly difficult to exclude a disease of unknown etiology without postmortem examination, the clinical picture had no resemblance to rheumatic fever as ordinarily encountered with the possible exception of the low-grade continuous type. There was no demonstrable latent period between the upper respiratory infection and the electrocardiographic findings and in spite of the persistence or increase in these findings, the patient never appeared ill. After the first few days there was a complete lack of concomitant evidence of rheumatic activity, such as fever, leukocytosis or increased sedimentation rate. They all manifested a persistent bradycardia after the acute phase of the illness had subsided. Polyarthritides or rheumatic nodules did not appear in a single individual. The systolic murmur, when audible, remained entirely unchanged throughout the period of observation. Moreover, the presence of hemolytic streptococci in the throats or cervical glands of patients with infectious mononucleosis was frequently described by the early investigators of this disease.^{55, 56} Indeed, the German clinicians were quite uniformly of the opinion that a streptococcus was the important etiologic agent.³ This view was based on the appearance of the throat, the predominance of streptococci in the flora of the upper respiratory tract and the occasional occurrence of a hemorrhagic nephritis or a scarlatiniform

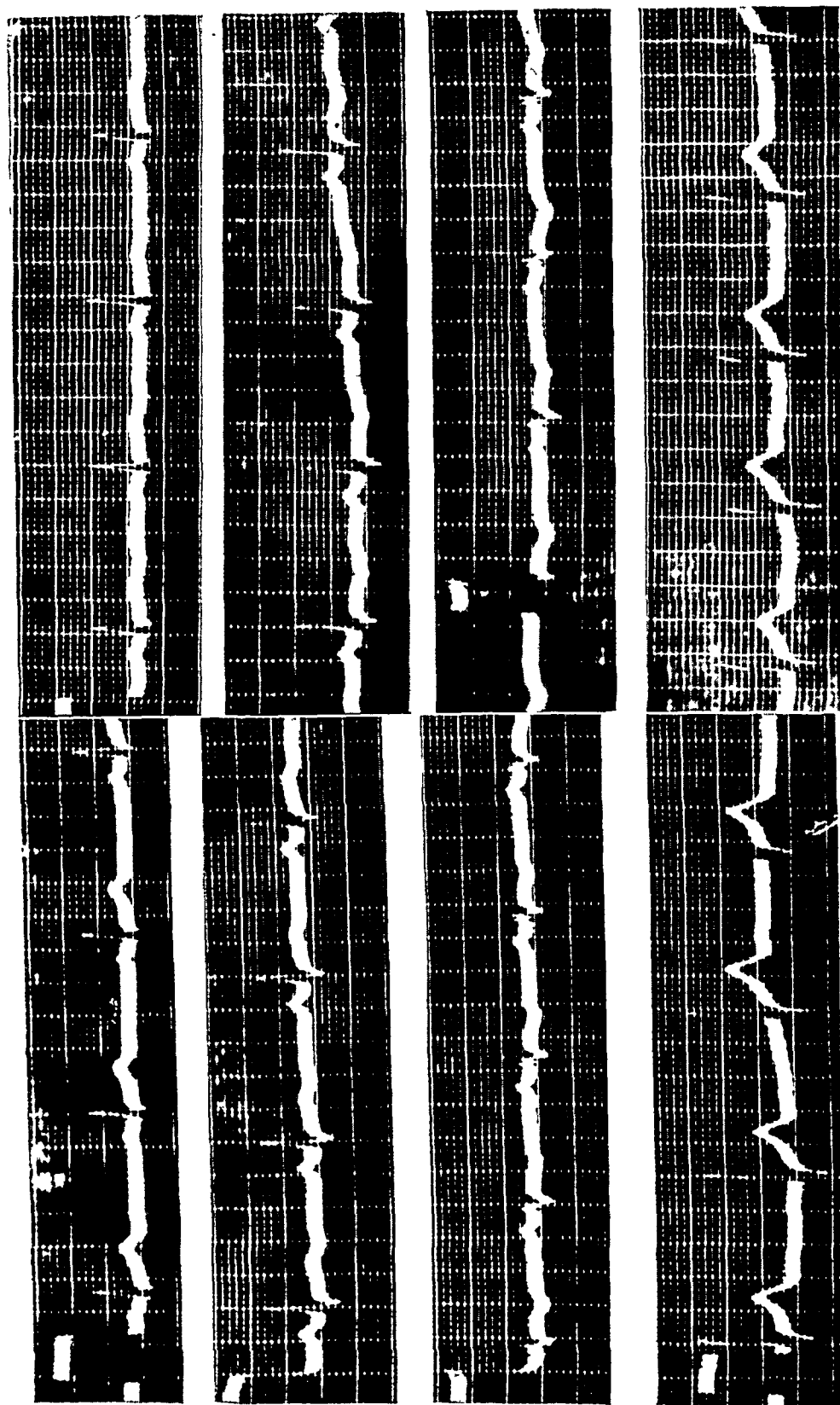


FIG. 11. (a) T₁ is normal and T₂ abnormally low. (b) The same patient, three weeks later. T₂ is now inverted and T₁ abnormally low.

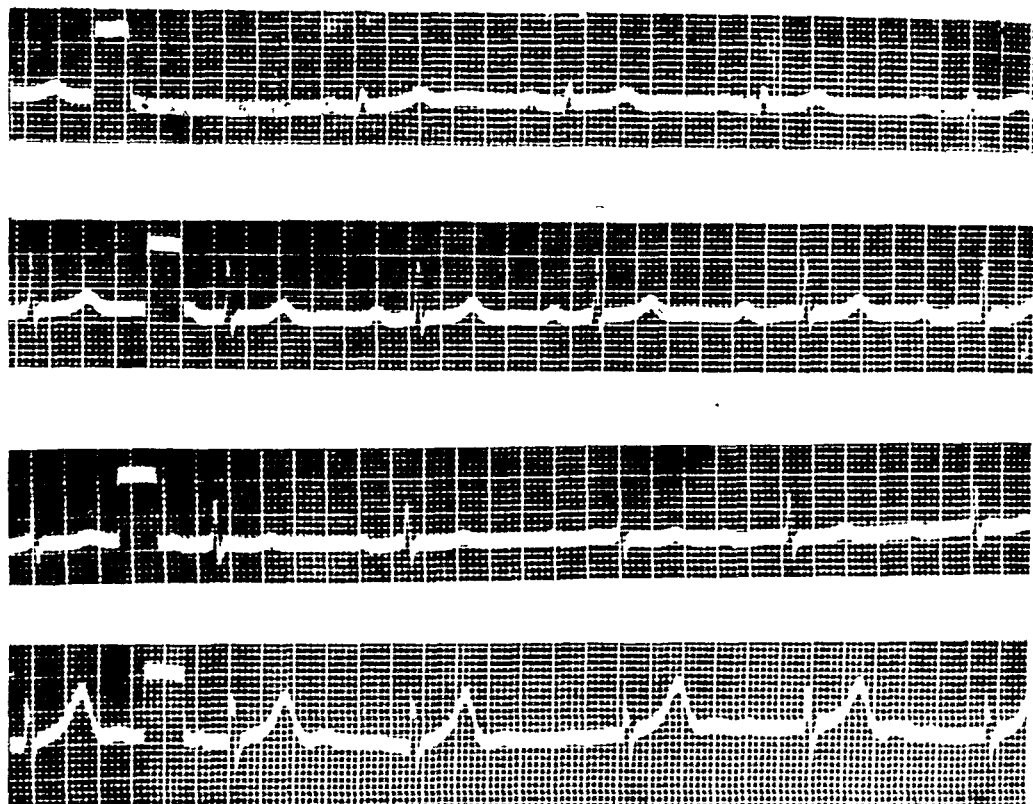


FIG. 12. The rate is 50. The P-R interval in Lead II increases progressively from 0.28 sec. to 0.40 sec.

eruption. In the more recent literature, cases have been reported that have been ushered in by a typical *beta* hemolytic streptococcus tonsillitis.^{10, 37} A rising anti-fibrinolysin titer in the circulating blood of a significant number of the group does not necessarily indicate more than the frequency with which these organisms acted as secondary invaders in infectious mononucleosis. Besides, a rising anti-fibrinolysin titer can be present in streptococcus sore throat, scarlet fever or rheumatoid arthritis without evidence of cardiac involvement.

It is tempting to ascribe the condition to an overactivity of the vagus nerve. A varying degree of vagotonia could explain the bradycardia, the absence of fever, leukocytosis and increased sedimentation rate, the prolonged P-R interval and the waxing and waning of the T-waves. A soft, systolic murmur at the apex is not an infrequent finding in neurocirculatory asthenia and in psychoneurotics with similar symptoms. Symptoms of neurocirculatory asthenia are known to occur after acute infections and prolonged P-R intervals and abnormal T-waves have been described in this syndrome.⁵⁷ However, one would have expected belladonna to have caused these changes to revert to normal. Belladonna was exhibited in increasing doses until toxic manifestations appeared and in some cases for long periods. Atropine, hypodermically, was not used. Even if it were granted that atropine in large

doses, hypodermically, might have abolished the electrocardiographic abnormalities, this in itself would not eliminate the possibility of myocardial involvement as it can abolish the prolonged P-R interval in rheumatic fever, where myocardial involvement is the rule.⁵⁸ Atropine has also abolished a recurrent complete heart block, yet autopsy showed a badly diseased bundle.⁵⁹

In conclusion, it can only be stated that although an autonomic imbalance is a strong possibility, actual involvement of the myocardium or its arteries cannot be excluded. Cases exhibiting the syndrome must be observed for many years and examined at post-mortem if possible, before the problem is finally elucidated.

12. Kidney. From the literature, the frequency with which the kidneys are involved in infectious mononucleosis varies greatly. Bernstein¹⁰ in his 65 cases had none, whereas Tidy and Morley⁵⁵ reported an incidence of 6 per cent in the 270 cases which they collected.

In our series, there were 17 cases with abnormal urinary findings or an incidence of 3 per cent. The abnormal constituents were red and white blood cells, albumin, and hyaline and granular casts. They occurred either at the onset or within the first week of the illness. The course was uniformly benign with rapid return to normal, usually within seven to 10 days. None developed oliguria, edema, elevated blood pressure, cardiac dilatation, nitrogen retention or impairment of urinary function. In two cases of frank hematuria, the intravenous pyelograms performed during convalescence were normal.

In four cases there was macroscopic hematuria. It occurred at the onset of the illness in all, persisted for two or three days, and was then followed by microscopic hematuria for five to seven days. Microscopic hematuria alone was reported in seven cases. One patient with microscopic hematuria developed a morbilliform rash, while another later developed jaundice.

Increased numbers of white blood cells were found in all. In one case the urine was loaded with pus cells and suggested a pyelitis.

The albuminuria, which was present in all of the 17 patients, varied between 1 plus and 4 plus. It was not always proportionate to the hematuria, as in five cases there were no red blood cells found. In one of the latter, the albumin was 4 plus.

Casts were present in small numbers. They were usually of the hyaline variety. Granular casts were found in five cases.

Throat cultures were taken in five of the cases. Three were positive for *Streptococcus hemolyticus*. Anti-fibrinolysin titers were not performed.

13. Skin. An extraordinary variety of exanthemata have been observed in this disease. Although macular and maculopapular eruptions are the most common, erythematous, urticarial, petechial, purpuric and vesicular types have also been described.^{10, 60} A case with lesions resembling erythema nodosum has been reported.⁶¹ The frequency with which these eruptions have appeared has varied considerably. In the London epidemic of 1930 an eruption was present in practically every case,^{62, 63, 64, 1 (1)} whereas in the re-

cent English epidemic² the incidence was only 4 per cent. In collections of sporadic cases, the incidence of eruptions has been as follows: Contratto,³³ 5.1 per cent; Sadusk,⁶⁰ 7 per cent; Bernstein,¹⁰ 9 per cent; Lyght,³² 17 per cent; Templeton and Sutherland,⁶⁵ 18.5 per cent.

Dermatologic manifestations occurred in 92 or 16 per cent of the patients in this epidemic. In an additional 16 patients a chronic dermatosis flared up or reappeared during the course of the illness. The eruptions were of many varieties and were often difficult to differentiate, especially when one variety blended into or followed another. We have classified the eruptions we have seen into the following types: (a) macular, (b) morbilliform and scarlatiniform, (c) maculopapular, (d) polymorphous, (e) nodular, (f) vesicular, (g) urticarial, (h) hemorrhagic, (i) alopecia.

a. Macular. This eruption appeared between the second and fourth day of the disease and was easily overlooked. There were two sub-types: a diffuse, red mottling, involving primarily the trunk and small faint-red macules scattered over the chest and abdomen and occasionally the extremities. The first type, of which there were four examples, faded very rapidly, usually within 24 hours. The second, of which there were five cases, closely resembled rose-spots, appeared in a single crop, blanched on pressure, were few in number and faded in a few days. There was no desquamation in either group.

b. Morbilliform and Scarlatiniform. This was the most frequent eruption and was also subdivided into two types. The first, consisting of 18 cases, was indistinguishable from the morbilliform rash of German measles. It appeared from the second to the fourteenth day of the disease. The lesions were numerous, diffuse, often confluent and involved both the trunk and extremities. As the clinical and hematological findings in German measles are so similar to those of infectious mononucleosis, the differentiation depended largely upon the Davidsohn absorption test. That it is impossible to distinguish between the two conditions in most instances without laboratory aid has been emphasized by other authors.^{60, 65, 66} It is of interest in this connection that Glanzmann,^{1 (d)} because of this similarity, postulated a close relationship between the viruses of the two diseases. It is in this group that the highest mononuclear counts were observed. In one case in which the disease occurred during convalescence from an acute cellulitis of the left foot, associated with lymphangitis and lymphadenitis of the femoral lymph nodes, the mononucleosis reached a peak of 95 per cent of a total white count of 19,300. In another, which occurred during convalescence from meningococcic meningitis in a patient who had the largest glands in this series, the mononucleosis was reported as 100 per cent of a total white count of 3,400. The second type, consisting of nine cases, was indistinguishable from that of classical scarlet fever, including a positive Schultz-Charlton test. As many of the clinical features of infectious mononucleosis, such as the sore throat, enlarged cervical lymph nodes, mild, generalized lymphadenopathy and a palpable spleen are, or can be, present in scarlet fever, the differentiation

depended upon the hematological and serological findings. The blood counts early in the disease were usually not conclusive, but serial blood counts revealed a progressive mononucleosis with large numbers of "leukocytoid" lymphocytes. This, in conjunction with a rising heterophile antibody agglutination titer and a positive Davidsohn absorption test, established the diagnosis. In eight of these nine cases, throat cultures were positive for *Streptococcus hemolyticus* and one wonders whether the scarlatiniform eruption was not due to secondary invasion by the streptococcus. *Streptococcus hemolyticus* was cultured from the throats of other patients with infectious mononucleosis during the period of this study, who did not develop this eruption, but it is well-known that streptococcus sore throat is accompanied by a rash in only a small percentage of cases. The positive Schultz-Charlton tests in every member of this group are difficult to explain on other grounds and militate against the possibility that an erythrotoxin is produced by the etiologic agent of infectious mononucleosis or by some other secondary invader. Unfortunately no anti-fibrinolysin or anti-streptolysin titers were performed in these cases. The eruption appeared with the onset of the disease in all but two cases, in whom it was delayed until the third and fourth day respectively. Typical desquamation occurred in all of the nine cases. Priest⁶⁷ described this phenomenon in one of his cases.

c. *Maculopapular*. There were 20 cases in this group. Although the lesions were discrete, they were not solitary and tended to have a patchy distribution on the upper and lower extremities as well as on the trunk. They were not so diffuse and symmetrically distributed as the morbilliform and scarlatiniform type, were more persistent and had an annular or circinate configuration. They closely resembled the eruptions of pityriasis rosea or secondary syphilis, but were considerably more pruritic than the usual examples of the former. The lesions usually appeared on the second or third day of the illness and in one of two forms. The first presented vari-sized, oval or rounded, scaling lesions with fine papular border and central clearing. They were quite profuse, especially on the extremities and were slightly more erythematous and had a heavier scale than the lesions of pityriasis rosea. The second variety exhibited vari-sized but larger, rounded, configurated lesions that had a tendency toward confluence with the formation of large patches. The centers were always macular and papular with a moderate or heavy scale and the borders at times showed signs of vesiculation. They were usually quite erythematous and were more pruritic than the first variety.

d. *Polymorphous*. There were 13 cases of this type. The lesions appeared from the first to the eighth day of the illness, and in a few were preceded by a morbilliform eruption. The lesions resembled those of erythema multiforme and were macular, papular, vesicular and occasionally bullous in character. They were profuse and involved the trunk, extremities, face and mucous membranes. The mucosal involvement, which was present at some time during the eruption in all, was occasionally severe, with extensive buccal

and gingival ulcerations. As a group, they represented the most serious skin manifestations and the patients were all very toxic.

c. Nodular. There were only two examples of this type. The lesions were typical of those seen in erythema nodosum and were confined to the anterior surfaces of the legs and knees. They appeared on the sixth and ninth day of the disease in these two cases and involuted with slight pigmentation and no scarring. In the case reported by Löhe and Rosenfeld,⁶¹ the lesions appeared three and one-half weeks after the onset of the illness.

f. Vesicular. This group consisted of 11 cases, six of herpes labialis, four of herpes progenitalis and one of herpes zoster. In the case with herpes zoster, grouped vesicular and bullous lesions on an inflammatory base extended from the origin of the twelfth rib near the spine around the left flank to just below the umbilicus. The herpes progenitalis at times was difficult to differentiate from primary syphilis, especially when complicated by an erosive balanitis. The latter occurred in two of these cases, and in one a false-positive Wassermann reaction added further difficulties.

g. Urticarial. Pruritus was a common but evanescent symptom in all cases with skin manifestations and often preceded the eruption, serving at times as a help in the differential diagnosis. In five cases urticaria was the only eruption, while in several others it was present before the onset of the other types of lesions. The wheals were not of the giant variety, but of the small papular type. They appeared in crops, usually very early in the illness and disappeared in from five to 14 days. Dermographism was a frequent finding.

h. Hemorrhagic. Hemorrhagic skin manifestations were rare although carefully sought. A few petechiae were found in three cases, on the lower extremities, the chest and back, respectively. One was associated with epistaxis and petechiae on the soft palate. Purpura was not encountered.

i. Alopecia. In two cases small bald spots in the scalp occurred in association with the illness. No history of emotional shock or other predisposing factors was elicited. The lesions took several months to clear up completely. This small group may have been merely a coincidental alopecia areata. We have included them in the skin manifestations, because they may represent a neurotropic involvement akin to the herpetic lesions or a symptomatic alopecia as a part of a systemic infection.

As would be expected in so large a series, infectious mononucleosis occurred in soldiers suffering from a great variety of skin diseases, and the effect of this illness on the latter is interesting. The lesions of acute dermatitis, dermatophytosis, scabies, psoriasis and lichen planus remained unaffected while those of the seborrheic and eczema-dermatitis group showed marked exacerbations or recurrences.

A biologic false-positive serologic reaction for syphilis occurred in only one of the entire group, a patient with a polymorphous eruption and pneumonia. All four of the cases with eruptions in the series reported by Sadusk⁶⁰ had a transiently positive reaction for syphilis and the author

believes that it is more apt to occur in such cases. In his study, the tests were repeated at frequent intervals, in some cases as often as every other day, as compared to the single examination performed in the great majority of our cases. In spite of this, one would have expected a larger percentage of positive tests if such a marked relationship existed between the two phenomena.

In conclusion, it may be pointed out that the great majority of the skin manifestations were of the type usually classified as toxic eruptions of dermal origin, and represented varying degrees of reaction on the part of the skin to toxins or allergens. Medication could be excluded in their etiology. All were treated symptomatically with the exception of the severely ill ones, such as those with polymorphous or scarlatiniform eruptions. In all of these, the skin lesions were already present when sulfadiazine was exhibited.

14. Central Nervous System. Involvement of the central nervous system has been known since 1931⁶⁸ and has been receiving increasing attention since that time. The situation, however, is confusing. The clinical picture is that of meningitis, encephalitis or both. It has been stated⁶⁹ that clinical signs of a serous meningitis may be present with normal spinal fluid findings and, conversely, that abnormal spinal fluids may be found in the absence of clinical signs of meningitis. It has also been reported⁷⁰ that the blood and spinal fluid findings may not occur until late in the course of the illness, so that early taps are not conclusive, and that clinical manifestations of infectious mononucleosis, such as lymphadenopathy and a palpable spleen, may not appear until the cerebral symptoms are almost gone.⁷¹ In addition, owing to the enlargement of the cervical glands, pain in the back of the neck is not infrequent. When this is severe, it may be accompanied by voluntary rigidity and simulate a meningitis.

In nine of our cases because of severe headache, usually frontal, and mild to moderate nuchal rigidity, a spinal tap was performed. The spinal fluid was normal in six. Of the remaining three, the spinal fluid contained 12 lymphocytes but was otherwise entirely negative in one. In another patient, who was semi-stuporous on admission, it was under increased pressure, while in the third, it showed definite and striking abnormalities. The spinal taps were not repeated in eight patients as the presenting symptoms and signs disappeared rapidly. The last case is cited in brief.

An Italian prisoner of war, 24 years of age, was admitted with a history of severe frontal headache and vomiting of three days' duration. His temperature was 100.6° F., and a follicular tonsillitis was present. His temperature dropped to normal on the second day and although he remained afebrile for five days, the headache not only persisted but became violent. It was associated with hyperirritability, hypersensitivity of the extremities and mild nuchal rigidity. He developed a severe stomatitis and gingivitis, smears from which were positive for Vincent's organisms. The anterior and posterior cervical, the supraclavicular and axillary nodes were enlarged and tender. The liver and spleen were not palpable. Neurological examination was negative except for slight haziness of the optic disc borders. A spinal tap, performed on the ninth hospital day, showed 524 white blood cells, 517 of which were lymphocytes. The

globulin was 4 plus; sugar, 104 mg. per cent; chlorides, 540 mg. per cent; total protein, 284 mg. per cent; colloidal gold, negative; Wassermann reaction, negative.

His headache was greatly relieved by the puncture, but continued to recur in such severity that it had to be repeated at frequent intervals and always with marked relief. The pleocytosis and increased protein gradually decreased. The final tap, performed on the sixtieth hospital day, showed 64 cells, of which 63 were lymphocytes. The globulin was negative, sugar 67 mg. per cent; total protein 34.6 mg. per cent; colloidal gold, 1111000000.

The white blood cell count, shortly after admission, was 24,500 with a differential of neutrophils 92 per cent, lymphocytes 7 per cent and monocytes 1 per cent. The white blood cells rapidly decreased to 9000, and the lymphocytes rose to 49 per cent, many of them "leukocytoid." The heterophile antibody agglutination titer rose to 1:224. There were no sequelae.

In summary, the clinical picture resembled that of lymphocytic choriomeningitis. The high total protein content of the spinal fluid would speak for cerebral involvement, although the neurological examination was negative for signs of localization. The initial spinal puncture, performed on the twelfth day of the disease, exhibited the most marked changes. The abnormalities of the spinal fluid then gradually diminished, the pleocytosis persisting for a longer time than the increased protein. A salient feature was the repeated relief of symptoms on withdrawal of spinal fluid and the relative well-being of the patient in spite of the severe headache.

The only other neurological manifestation was a severe, right brachial neuritis in a white officer, 29 years of age. He was admitted with a history of sore throat, chills, fever and 'dizziness of four days' duration. The pharynx was injected, the cervical glands markedly enlarged and the spleen palpable. His temperature on admission was 104° F. and then gradually subsided to normal on the fifth hospital day. The highest mononucleosis was 72 per cent and the maximum heterophile antibody agglutination titer was 1:1792. The brachial neuritis made its appearance on the seventh hospital day. He was treated with physiotherapy, large doses of vitamin B₁ and sedatives and the symptoms cleared completely in two weeks. A spinal tap was not done.

15. Other Organs. Although scleral injection was frequent, an actual conjunctivitis was recorded in only 12 instances. It occurred early in the course of the disease and was follicular in character. Rarely, the bulbar conjunctiva was fiery red and was accompanied by photophobia.

The salivary glands, testes and thyroid were not involved in any case.

16. Relapses. A relapse occurred in 50 patients or 9 per cent of the series. A second relapse took place in four. The duration of the afebrile period for the 54 relapses varied between one and 27 days. The interval between the attacks for all relapses is shown in table 6. Relapses were most frequent during the first week, when 65 per cent occurred. The relapses were usually milder than the original attack and followed the same pattern. Occasionally, however, they were more severe and new manifestations ap-

peared. In one case, a scarlatiniform eruption appeared with the relapse. The duration of fever in the relapse varied between one and 11 days.

17. *Incubation Period.* There is a wide divergence of opinion concerning the period of incubation.¹⁰ The accumulation of reliable data relating to this period during the epidemic presented certain difficulties. In a disease as widespread as this and containing a great many insidious and mild cases, the possibilities for contact were obviously numerous. Acute attacks of infectious mononucleosis occurred in patients hospitalized for other conditions but here also, multiple exposures could not be excluded. It has already been stated that practically every patient in the hospital at the height of the epidemic showed some abnormal lymphocytes on blood smear. It was, therefore, decided to determine the interval between the arrival of the organization on the post and the earliest appearance of the disease among its members. There were many such organizations who arrived after the epidemic was in progress and in the great majority of these, this interval was

TABLE VI
Relapses

Days Afebrile	Number of Cases	Days Afebrile	Number of Cases	Days Afebrile	Number of Cases
1	6	10	1	19	2
2	8	11	2	20	2
3	5	12	0	21	1
4	6	13	1	22	0
5	4	14	1	23	0
6	2	15	2	24	2
7	2	16	1	25	1
8	2	17	2	26	0
9	2	18	0	27	1

nine days. In a few, cases occurred as early as seven or eight days. As the day of onset of the disease was usually not the day of admission to the hospital, the patient's history had to be utilized in most instances.

18. *Laboratory Findings. A. Blood.* Before discussing the hematological findings, it must be reiterated that the patients were admitted to the hospital in various stages of the illness, that a considerable number were asymptomatic and that many had but one or two blood counts. Our analysis, therefore, cannot be compared to the published collections of sporadic cases, which consisted almost entirely of those with such marked clinical manifestations that the disease was suspected or recognized and which were usually studied more completely.

The initial, total leukocyte count for the entire series was between 6,000 and 9,000 in 46 per cent, above this level in 34 per cent and below it in 20 per cent. A better conception of the behavior of the leukocyte count is gained by the exclusion of the insidious cases and the tabulation of the acute cases according to the day of the disease in which the primary blood count was performed. The typical sequence was an initial, transient leukocytosis.

varying between 10,000 and 20,000, or a normal count followed by a drop to either normal or leukopenic values. With these initial counts, the percentage of neutrophils was usually normal or elevated. It rarely reached 90 per cent. A leukopenia and granulocytopenia at the very onset of the disease were unusual. This is at variance with the findings of Paul¹² in his sporadic cases. On the other hand, some sporadic cases have had a similar hemogram.^{10, 33, 45} Blood counts in sporadic cases are usually not performed until four or five days after symptoms have appeared¹⁰ and it is possible that a transient polymorphonuclear leukocytosis is missed. In the epidemics described by Glanzmann^{1 (d)} and by Guthrie and Pessel,^{1 (e)} an initial polymorphonuclear leukocytosis was the rule. Where leukopenia ensued, or was present on the initial count, the leukocytes gradually increased to normal and not infrequently to higher levels. The highest leukocyte count was 32,000 and occurred in two cases. The highest leukocyte counts attained in all

TABLE VII
Highest Leukocyte Count

Leukocyte Count	Percentage of Cases
Below 6,000	7.6
6-8,000	29.4
8-10,000	27.3
10-12,000	13.8
12-15,000	12.8
15-20,000	7.4
20-25,000	0.9
25-30,000	0.4
over 30,000	0.4

cases are shown in table 7. It will be observed that in spite of the factors already enumerated, the leukocyte count exceeded 10,000 in 35.5 per cent.

While the initial leukocytosis, when present, usually lasted for but a few days, the leukopenia tended to persist for a week or longer. The fall in the neutrophils was more rapid than that of the total leukocyte count. There were 20 cases with counts of 4,000 or below. The lowest leukocyte count was 3,000. The leukopenia was due chiefly to a reduction in the absolute neutrophil count. Their number ranged from zero to 2900 cells, while their percentage varied between zero and 78 per cent. A concomitant reduction in the mononuclear elements was occasionally present. In four cases, the absolute mononuclear count was below 1,500. For the entire leukopenic group, the mononuclear cells varied between 777 and 3,485 and their percentages between 21 and 100 per cent. The average for these cells was 58 per cent.

The neutropenia was not confined to the leukopenic counts but was frequently present with normal and occasionally with markedly elevated leukocyte counts. There were 15 examples of leukocytosis with granulopenia. In one case, with a total leukocyte count of 19,300, the neutrophils numbered

only 965 and in another, with 32,000 leukocytes, the neutrophils were reduced to 3,840. In the entire series, there were four cases in which the total number of myeloid cells fell below 1,000. The actual figures for these cases were: 0; 60; 310; 965.

During the early stages of the disease, the eosinophils were either absent or present in small numbers. During convalescence, they were frequently increased. There were 74 cases with an eosinophilia of 6 per cent or over. In 17 of these, however, other conditions were present that are frequently accompanied by an eosinophilia, viz. skin diseases, especially scabies and eczema, 12; asthma and hay fever, 3; uncinariasis, 2. The upper limit of the eosinophilia was 26 per cent in an asthmatic. Excluding this case, there were five with percentages of 15 or over for which no other cause could be demonstrated. The highest figure was 21 per cent.

The increase in mononuclear cells was usually evident after the third day of the disease but not infrequently this was delayed, so that the peak of the

TABLE VIII
Degree of Mononucleosis

Mononuclear Percentage	Percentage of Cases
Below 40	30
40-50	38
50-60	19
60-70	7
70-80	3
80-90	1.5
90-100	1.5

mononucleosis was not reached until the second or third week. The maximum degree of mononucleosis in our cases is shown in table 8. The reasons for the preponderance of low values have already been stated. If the insidious cases and those with but a single observation are excluded, the percentages more closely parallel those for sporadic cases.

The abnormal or "leukocytoid" lymphocytes need not be described as their distinctive features have already been discussed by many authors.^{1 (d), 3, 28, 46, 73, 74} To have been included in this series, each case must have exhibited at least 10 per cent of the total leukocyte count in the form of these abnormal lymphocytes. In the great majority, the percentage of these cells was higher than 10 per cent and in many the percentage was 50 or more. In conjunction with the mononucleosis these cells usually diminished slowly over a period of weeks but were present in small numbers long after the mononucleosis had disappeared in those cases who were observed for long periods of time.

An anemia of any appreciable degree did not appear in any case in this series. The lowest recorded count was: red blood cells 4 million; hemoglobin 75 per cent (Sahli). Platelet counts and bleeding and clotting times were performed in only five cases and were normal in all.

B. Heterophile Antibody Agglutination. The highest titers in the 556 cases are shown in table 9. If an agglutination in a dilution of 1:112 or over is considered as significant, the test was positive in 62 per cent. The highest titer was 1:28,672. A rising titer was present in 236 cases. In judging these values, the fact that many had only a single determination and that no attempt was made to determine the maximum attainable titer, must be taken into consideration.

The time of appearance of a significant titer was erratic. Although it is true that a titer of 1:112 or higher was frequently observed during the first week of the disease, it, just as frequently, took two to four weeks for this to occur. A strongly positive reaction was invariably present early in the course of the disease in the group with maximum titers of 1:1,792 or higher. The rise in the titer was occasionally very abrupt and we have observed an increase from 1:56 to 1:448 or 1:896 within two days. In the cases that were under prolonged observation for either cardiac involvement or other conditions, there were several with titers of 1:112 and 1:224 six months after the onset of the illness.

TABLE IX
Heterophile Antibody Agglutinin Titer

Titer	Percentage of Cases	Titer	Percentage of Cases
1:7	2	1:448	6
1:14	6	1:896	3
1:28	9	1:1,792	2
1:56	21	1:3,584	1
1:112	35	1:7,168	1
1:224	14	1:28,672	1

Davidsohn absorption tests,^{30, 75} using both guinea-pig kidney and boiled beef red corpuscles, were performed at random, in doubtful cases with low titers and in patients with jaundice or with morbilliform eruptions. Although this test was strikingly confirmatory in many, it was not uniformly satisfactory. In a number of cases in which the guinea-pig kidney did not completely absorb the agglutinins, the beef red cells likewise failed to do so and in some of these, the latter absorbed a smaller percentage of the agglutinins than did the guinea-pig suspensions. In others, although there was no previous history of serum disease or recent injections of serum, both suspensions completely absorbed the sheep cell agglutinins. These cases were otherwise indistinguishable from the others in this series both clinically and hematologically and the titers before absorption were occasionally as high as 1:896. We have no explanation for these phenomena. One might infer that the heterophile agglutinins in this epidemic differed from that described for sporadic cases or that they varied in character with the stage of the disease. No experiments to clarify these suppositions were undertaken. Although Davidsohn absorption tests have been performed in a relatively small number of sporadic cases, similar irregularities have ap-

parently been encountered. Demanche²⁹ reported that in one of his cases of infectious mononucleosis there was no absorption by either antigen, while in another, an affinity for the beef red cells took place only after 24 hours. A study of the 78 absorption tests reported by Kaufman¹³ reveals that 12 of the supposedly confirmatory tests were actually negative. In 10 of these, the sheep cell agglutinins were completely absorbed by both antigens. The test became positive later in the course of the disease in one of this group. Both of the other two showed complete absorption by the guinea-pig kidney suspension and incomplete absorption by the beef red cell suspension in one and no absorption in the other. There is some evidence^{4, 76} that the titer of the normal Forsmann sheep cell agglutinins may increase before the development of the heterophile antibody typical of infectious mononucleosis.

C. Other Antibodies. The occurrence of a false-positive Widal test and increased agglutinins for various other bacteria have been reported.²⁵ In table 10 are shown the agglutinin titers for the bacteria tested and the number

TABLE X
Bacterial Agglutinin Titers

Titer	<i>E. typhosa</i>	<i>S. paratyphi</i> A	<i>S. paratyphi</i> B	<i>Br. melitensis</i>	Proteus OX19	<i>Past.</i> <i>tularensis</i>
0	54	67	59	19	11	3
1-20	3	2	1	—	1	—
1-40	6	1	1	—	—	—
1-80	2	1	3	1	—	—
1-160	4	—	2	—	—	—
1-320	1	1	3	—	—	—
1-640	4	—	3	1	1	—
1-1280	1	—	—	—	—	—
Total	75	72	72	21	13	3

of cases in which these tests were performed. The 75 cases were chosen at random. All had the Widal test but the other agglutinin titers were done in smaller and varying numbers. Significant agglutinins were found against all the bacteria tested, except for *Pasteurella tularensis*. However, only three sera were tested with this organism. Titers of 1:160 or higher were found in 13 per cent of the sera tested with *E. typhosa* and in 15 per cent of those with *S. paratyphi* B. In a number of cases, repeated titrations were done and it was noted that the titer rose abruptly and was transient. In one case, eight days after a negative test, the agglutinins were: *E. typhosa*, 1:1280; *S. paratyphi* A, 1:320; and *S. paratyphi* B, 1:160. In another case, a Widal of 1:640 decreased to 1:80 nine days later. All of the soldiers had received at least three injections of the Army's triple typhoid vaccine some time in the past. A so-called anamnestic reaction could explain the frequency with which high agglutinin titers for typhoid and paratyphoid were encountered in the group tested.

D. Kahn and Wassermann Reactions. Biologic false-positive reactions for syphilis in both the sporadic and epidemic forms of the disease are known

to occur. The first case was reported by Löhe and Rosenfeld⁶¹ in 1928. Since that time, there have been numerous reports of such cases.^{10, 36, 44 (b), 60, 63, 64, 66, 67, 77} Kolmer and his co-workers^{77 (g)} compiled these publications and found transiently positive reactions in 20.9 per cent of 191 cases subjected to a Wassermann test and in 11.6 per cent of 146 cases subjected to a flocculation test. These figures, however, are misleading for several reasons. The two doubtful cases reported by Radford and Rolleston^{78, 79} are included and the same three cases reported by Weber⁶³ and by Weber and Bode^{77 (a)} are listed separately. Only two small collections with entirely negative findings^{27, 80} are tabulated. Most vitiating is the inclusion of mere case reports for as Davis⁷⁹ points out, such cases enjoy a low threshold of publication.

The incidence in the small groups of sporadic cases reported has varied markedly as follows: Kaufman,^{77 (d)} 3.6 per cent; Saphir,^{77 (e)} 10 per cent; Sadusk,⁶⁰ 13 per cent; Bernstein,¹⁰ 18 per cent. The epidemic cases have shown even more divergence. Tidy⁶² stated that a transiently positive Wassermann reaction was present in about 50 per cent of the cases in the London epidemic of 1930 and Gooding⁶⁴ reported a positive reaction in 59 per cent of 27 cases from that epidemic. In the recent English epidemic the Wassermann and Kahn reactions were consistently negative in the many patients tested,² although the authors do not give the actual number of such tests.

These conflicting reports are probably due to variations in the sensitivity of the tests employed and the frequency and regularity with which they were performed. Many false-positives, according to Davis,⁷⁹ are technical and due to excessive sensitivity. Because adequate standardization had not yet become widespread, he considers as unreliable all papers on this subject written prior to 1930. Even with our improved methods, there is considerable fluctuation in sensitivity and a single positive report cannot be considered as valid evidence of a false-positive reaction. The diagnostic criterion he advocates is a repeatedly positive reaction to more than one kind of test or to the same test in two different laboratories that becomes negative after a few weeks or months without antisyphilitic treatment.

False-positive reactions ordinarily appear during the second week of the disease, although they can occur earlier.⁶⁰ The importance of frequent testing as against a single examination on admission was emphasized by Sadusk.⁶⁰ In his series, the incidence rose from 8 to 13 per cent when repeated tests at regular intervals were instituted. It is usually weak⁷⁹ and reverts to negative within two weeks, although occasionally it may persist as long as three months.⁶⁰ The Army recommends⁸¹ that the patients be followed serologically and without treatment for a period of three months, serologic tests being performed every two to four weeks. At the end of this period, those that have reverted to negative are discharged from observation as non-syphilitic, those that are persistently positive are regarded as syphilitic, while those showing conflicting serologic reactions are subjected to further observation and study.

A blood Kahn test was performed in 263 patients. In the majority of cases, the blood was drawn at the end of the first week or during the second week of the disease. In the remainder, the duration of the illness was unknown owing to its insidious character or the test was done more than two weeks after its onset. The test was repeated in only 10 per cent of those with negative reports. A blood Wassermann test was performed in those with positive or doubtful Kahns and the tests were re-duplicated by our laboratory and by the Service Command Laboratory. Both tests were then repeated at frequent intervals.

The Kahn test was positive in eight and of these, the Wassermann test was positive in four and negative in four. The Kahn was doubtful in four and of these, the Wassermann was positive in two, doubtful in one and negative in one. None of the cases had been recently vaccinated. In four of the 12 cases, however, there was a history of a positive serologic reaction and antisyphilitic treatment in the past. Although these reactions were also transient, we feel that they should be excluded as they may represent the irregular behavior of weakly positive syphilitic sera. This reduces the incidence from 4.5 to 3 per cent. Because of the lack of repeated tests in those cases with initial negative reports, this cannot be regarded as the actual incidence of the phenomenon in this epidemic.

The reaction was transient in all. The shortest duration was nine days and the longest, 101 days. In those patients in whom the positive reaction persisted for longer than a few weeks, its intensity gradually diminished. The highest Wassermann titer was 12 units. Kahn verification tests revealed a biologic reaction in the three cases in which they were performed.

E. Bacteriological. Blood cultures were taken in 15 cases and were uniformly negative.

There were records of throat cultures in 104 patients. Of these, 61 were negative and 43 were positive for hemolytic streptococci, an incidence of 41 per cent. The anti-fibrinolysin titers in those cases with abnormal electrocardiograms have already been described.

Smears for Vincent's organisms were performed in 111 cases with positive findings in 74 or 67 per cent.

F. Miscellaneous. The laboratory studies carried out in the icteric group, the urinary findings and the changes in the cerebrospinal fluid have already been described in the appropriate sections.

Non-protein nitrogen, serum protein and serum calcium and phosphorus were determined in three cases and were all within normal limits.

The erythrocyte sedimentation rate was usually slightly or moderately elevated in the acute cases if tested during the febrile stage. The usual rate ranged between 12 and 35 mm. in one hour and fell rapidly to normal with convalescence. The highest rate was 79 mm.

19. Therapy. Sulfadiazine, in doses of 2 grams initially and 1 gram every four hours thereafter, was used in approximately half of the cases of the anginose type and in all with pulmonary symptoms, scarlatiniform

eruptions or positive hemolytic streptococcus throat cultures. It is difficult to analyze the results in a disease which is so variable in its severity, course and duration. It did not produce any spectacular response and there was no significant effect upon the duration of the disease in the treated group.

Penicillin was exhibited in one case not included in this series. He had a severe ulcerative tonsillitis, marked generalized lymphadenopathy, enlarged liver and spleen, mild jaundice and a morbilliform rash. Throat smears were positive for Vincent's organisms and cultures showed *Streptococcus hemolyticus*. He was given 2,340,000 units in a period of nine days with no appreciable effect on the clinical course or the hematological findings and only temporary disappearance of the positive throat cultures.

All acute cases were treated with bed rest, soft diet, forced fluids, sodium perborate mouth washes and small doses of aspirin. When jaundice was present, the patients were placed on low fat, high carbohydrate diets and multi-vitamin capsules.

SUMMARY

A study of an epidemic of infectious mononucleosis in an army post is presented based on 556 cases observed during a period of 15 months. The diagnostic criteria and their limitations are discussed. An arbitrary standard, the presence of a least 10 per cent of the total white cell count in the form of abnormal lymphocytes, was used as the basis for the inclusion of the cases analyzed in this study.

The epidemic had many unusual features. Among these were the large number of asymptomatic cases, the incidence of the disease among the negro soldiers, the frequency and type of pulmonary involvement, the finding of electrocardiographic abnormalities in a large percentage, the number and variety of eruptions encountered and the irregularities in the results of the Davidsohn absorption test. In other respects, the disease closely resembled the sporadic form, the differences for the most part being due to the inclusion of insidious cases and the lack of serial blood studies in many of the patients.

The incubation period, as determined by the shortest interval between the appearance of symptoms and the arrival of the soldiers on the post, was seven to nine days. The disease attacked all ages of the select group involved. The percentage incidence at ages 18 to 20 inclusive was significantly greater and after age 38, significantly lower than the percentage strength of these ages in the army as whole, during the period of the epidemic. The divergence was most marked at age 18. Negroes were more susceptible to the disease.

The protean manifestations and the systemic nature of the disease are well illustrated, as are its contagiousness, its tendency to relapse and its generally benign course. The similarity between the pneumonitis complicating infectious mononucleosis and "virus" pneumonia was marked. The clinical picture and the liver function tests in the icteric group indicated that a dif-

fuse hepatitis was responsible for the jaundice. The impossibility of differentiating this group from infectious hepatitis without the aid of the heterophile antibody agglutination test was stressed. This was also true in excluding German measles and scarlet fever in those cases with eruptions characteristic of these diseases. Evidence is presented in support of the view that the scarlatiniform eruption was the result of secondary invasion by *Streptococcus hemolyticus*. Electrocardiographic abnormalities were frequent. The typical hemogram was an initial leukocytosis or normal count followed by a drop to normal or leukopenic values associated with a rising mononucleosis. Biologic false-positive serologic tests for syphilis were not of frequent occurrence. Sulfadiazine therapy had no appreciable effect upon the course of the disease.

No information was gleaned as to the etiology of the disease. Indeed, many other problems were raised by this study, especially the possible relationship between some of the clinical manifestations and secondary invasion with hemolytic streptococci, the nature of the pulmonary and cardiac lesions and the cause for the erratic behavior of the heterophile antibody agglutinins in the differential absorption tests. We hope that opportunity for future studies will clarify these problems.

BIBLIOGRAPHY

1. (a) BURNFORD, J.: A note on epidemics, *Brit. Med. Jr.*, 1918, ii, 50.
- (b) BURNS, J. E.: Glandular fever. Report of an epidemic in the children's ward of the Union Protestant Infirmary, *Arch. Int. Med.*, 1909, iv, 118.
- (c) DAVIS, C. M.: Acute glandular fever of Pfeiffer. Report of a nursery epidemic, *Jr. Am. Med. Assoc.*, 1929, xcii, 417.
- (d) GLANZMANN, E.: Das lymphamoide Drüsenfieber, *Jahrb. f. Kinderh.*, 1931, cxxxii, 1.
- (e) GUTHRIE, C. C., and PESSEL, J. F.: An epidemic of "glandular fever" in a preparatory school for boys, *Am. Jr. Med. Sci.*, 1925, xxix, 492.
- (f) MILLS, J.: Glandular fever, *Roy. Berkshire Hosp. Rep.*, 1932, p. 66.
- (g) NOLAN, R. A.: Report of so-called glandular fever (infectious mononucleosis), *U. S. Nav. Med. Bull.*, 1935, xxxiii, 479.
- (h) SCHEER, K.: Eine Epidemie des Pfeifferschen Drüsenfiebers, *Monatschr. f. Kinderh.*, 1930, xlviii, 59.
- (i) SCHULZ, E.: Eine Epidemie von Pfeifferschen Drüsenfieber, *München. med. Wchnschr.*, 1933, lxxx, 1809.
- (j) TIDY, H. L., and DANIEL, E. C.: Glandular fever and infective mononucleosis with an account of an epidemic, *Lancet*, 1923, ii, 9.
- (k) WEST, J. P.: An epidemic of glandular fever, *Arch. Pediat.*, 1896, xiii, 889.
2. HALCROW, J. P. A., OWEN, L. M., and RODGER, N. C.: Infectious mononucleosis with an account of an epidemic in an E. M. S. hospital, *Brit. Med. Jr.*, 1943, ii, 443.
3. BALDRIDGE, C. W., ROHNER, F. J., and HANSMANN, G. H.: Glandular fever (infectious mononucleosis), *Arch. Int. Med.*, 1926, xxxviii, 413.
4. WARREN, E. W.: Observations on infectious mononucleosis, *Am. Jr. Med. Sci.*, 1941, cci, 483.
5. RANDOLPH, T. G., and GIBSON, E. B.: Blood studies in allergy. II. The presence in allergic disease of atypical lymphocytes and symptoms suggesting the recovery phase of infectious mononucleosis, *Am. Jr. Med. Sci.*, 1944, ccvii, 638.

6. RANDOLPH, T. G., and HETTIG, R. A.: The coincidence of allergic disease, unexplained fatigue, and lymphadenopathy; possible diagnostic confusion with infectious mononucleosis, *Am. Jr. Med. Sci.*, 1945, ccix, 306.
7. FARLEY, D. L.: Acute infectious mononucleosis, *Med. Clin. N. Am.*, 1937, xxi, 1139.
8. JONES, C. M., and MINOT, G. R.: Infectious (catarrhal) jaundice. An attempt to establish a clinical entity. Observations on the excretion and retention of the bile pigments, and on the blood, *Boston Med. and Surg. Jr.*, 1923, clxxxix, 531.
9. BARKER, M. H., CAPPS, R. B., and ALLEN, F. W.: Acute infectious hepatitis, *Jr. Am. Med. Assoc.*, 1945, cxxviii, 997.
10. BERNSTEIN, A.: Infectious mononucleosis, *Medicine*, 1940, xix, 85.
11. GILBERT, R., and COLEMAN, M. B.: Laboratory findings in an epidemic of glandular fever, *Am. Jr. Hygiene*, 1925, v, 35.
12. PAUL, J. R., and BUNNELL, W. W.: The presence of heterophile antibodies in infectious mononucleosis, *Am. Jr. Med. Sci.*, 1932, clxxxiii, 90.
13. KAUFMAN, R. E.: Heterophile antibody reaction in infectious mononucleosis, *Ann. Int. Med.*, 1944, xxi, 230.
14. HIMSWORTH, H. P.: Infective mononucleosis and the Paul-Bunnell test, *Lancet*, 1940, i, 1082.
15. FOORD, A. G., and BUTT, E. M.: The laboratory diagnosis of infectious mononucleosis, *Am. Jr. Clin. Path.*, 1939, ix, 448.
16. BARRETT, A. M.: The serological diagnosis of glandular fever (infectious mononucleosis): a new technique, *Jr. Hygiene Camb.*, 1941, xli, 330.
17. HIMSWORTH, H. P.: Vagaries of the Paul-Bunnell test, *Lancet*, 1941, i, 195.
18. ISRAELS, M. C. G.: Paul-Bunnell test in glandular fever, *Lancet*, 1941, i, 260.
19. KENT, C. F.: "False" positive Paul-Bunnell (heterophile) reaction?, *Am. Jr. Clin. Path.*, 1940, x, 576.
20. BORNSTEIN, S.: Heterophile antibody reaction caused by bacterial infection, *Ann. Int. Med.*, 1942, xvi, 472.
21. BEEUKES, H.: De reactie van Paul en Bunnell, *Nederl. tijdschr. v. geneesk.*, 1939, lxxxiii, 149.
22. DAVIDSOHN, I.: Heterophile antibodies in serum disease: third report, *Jr. Infect. Dis.*, 1933, xliii, 219.
23. SMEALL, J. T.: Glandular fever (infectious mononucleosis), *Edinburgh Med. Jr.*, 1930, xlix, 59.
24. SHAW, R. M., and MACGREGOR, J. N.: The Paul-Bunnell test for infectious mononucleosis, *Canad. Pub. Health Jr.*, 1934, xxv, 553.
25. BERNSTEIN, A.: Antibody responses in infectious mononucleosis, *Jr. Clin. Invest.*, 1934, xiii, 419.
26. BUNNELL, W. W.: A diagnostic test for infectious mononucleosis, *Am. Jr. Med. Sci.*, 1933, clxxxvi, 346.
27. BUTT, E. M., and FOORD, A. G.: The heterophile antibody reaction in the diagnosis of infectious mononucleosis, *Jr. Lab. and Clin. Med.*, 1935, xx, 538.
28. STUART, C. A., BURGESS, A. M., LAWSON, H. A., and WELLMAN, H. E.: Some cytologic and serologic aspects of infectious mononucleosis, *Arch. Int. Med.*, 1934, liv, 199.
29. DEMANCHE, R.: Le diagnostic de la mononucléose infectieuse: valeur des réactions sérologiques, *Press. med.*, 1939, xlvii, 1614.
30. DAVIDSOHN, I.: Serologic diagnosis of infectious mononucleosis, *Jr. Am. Med. Assoc.*, 1937, cviii, 289.
31. STRAUS, R., and BERNSTEIN, M. T.: Further serological studies in infectious mononucleosis, *Am. Jr. Clin. Path.*, 1942, xii, 174.
32. LYGH, C. E.: Infectious mononucleosis, *Journal-Lancet*, 1938, lviii, 91.
33. CONTRATTO, A. W.: Infectious mononucleosis. A study of 196 cases, *Arch. Int. Med.*, 1944, lxxiii, 449.
34. MOIR, J. I.: Glandular fever in the Falkland Islands, *Brit. Med. Jr.*, 1930, ii, 822.

35. LONGCOPE, W. T.: Infectious mononucleosis (glandular fever) with a report of 10 cases, *Am. Jr. Med. Sci.*, 1922, clxiv, 781.
36. WERLIN, S. J., DOLGOPOL, V. B., and STERN, M. E.: Infectious mononucleosis—a diagnostic problem, *Am. Jr. Med. Sci.*, 1941, cci, 474.
37. RAY, E. S., and CECIL, R. C.: Infectious mononucleosis in the negro. Report of three cases with one complicated by sickle cell anemia, *South. Med. Jr.*, 1944, xxxvii, 543.
38. JOHNSON, R. D.: Infectious mononucleosis in the negro. Report of two cases in children, *Jr. Am. Med. Assoc.*, 1944, cxxviii, 1255.
39. BLAIN, A., and VONDER HEIDE, E. C.: Infectious mononucleosis and the negro. With a report of 6 cases, *Am. Jr. Med. Sci.*, 1945, ccix, 587.
40. YOUNG, L. E., STOREY, M., and REDMOND, A. J.: Clinical and epidemiological features of an outbreak of primary atypical pneumonia of unknown etiology among hospital and medical school personnel, *Am. Jr. Med. Sci.*, 1943, ccvi, 756.
41. MACKEY, R. D., and WAKEFIELD, E. G.: The occurrence of abnormal lymphocytes in the blood of a patient with jaundice (infectious mononucleosis-glandular fever), *Ann. Clin. Med.*, 1926, iv, 727.
42. DOWNEY, H., and MCKINLAY, C. A.: Acute lymphadenosis compared with acute lymphatic leukemia, *Ann. Int. Med.*, 1923, xxxii, 82.
43. SPRING, M.: Jaundice in infectious mononucleosis, *Bull. U. S. Med. Dept.*, 1944, lxxxi, 102.
44. (a) SVAAR-SELJAESTER, O.: Icterus og infektiøs mononukleose, *Nordisk Medicin*, 1939, iv, 3517.
- (b) FOWLER, W. M., and TIDRICK, R. T.: Unusual manifestations of infectious mononucleosis, *Am. Jr. Clin. Path.*, 1940, x, 548.
- (c) MARTIN, L.: Glandular fever with jaundice. Report of 2 cases, *Lancet*, 1941, ii, 481.
- (d) FEIL, L.: Ein Beitrag zur Frage des lymphämoiden Drüsenfiebers, *Schweiz. med. Wchnschr.*, 1941, lxxi, 1071.
- (e) GOLD, S.: Glandular fever with jaundice, *Lancet*, 1942, i, 102.
- (f) RYAN, J. M.: Infectious mononucleosis, *Minnesota Med.*, 1942, xxv, 871.
- (g) HOWARD, R. P.: Infectious mononucleosis with jaundice, *Canad. Med. Assoc. Jr.*, 1942, xlvii, 464.
- (h) MARTIN, L.: Glandular fever with jaundice, *Lancet*, 1942, i, 153.
- (i) CARTER, A. B.: Glandular fever with jaundice, *Lancet*, 1942, i, 102.
- (j) LEAVELL, B. S., and McNEEL, J. O.: Infectious mononucleosis: Unusual manifestations, *Virginia Med. Monthly*, 1942, lxi, 180.
- (k) STIEFEL, H.: Zur Frage der Mononucleosis infectiosa beim Erwachsenen: an Hand von 78 sporadischen Fällen, *Folia haemat.*, 1943, lxvii, 61.
- (l) ZIEGLER, E. E.: Infectious mononucleosis. Report of a fatal case with autopsy, *Arch. Path.*, 1944, xxxvii, 196.
- (m) MORRIS, M. H., ROBBINS, A., and RICHTER, E.: Acute infectious mononucleosis with hepatitis. Presentation of two cases, *New York State Jr. Med.*, 1944, xiv, 1579.
- (n) PRESS, J. H., SHLEVIN, E. L., and ROSEN, A. P.: Infectious mononucleosis; a study of 96 cases, *Ann. Int. Med.*, 1945, xxii, 546.
45. MCKINLAY, C. A.: Infectious mononucleosis, *Jr. Am. Med. Assoc.*, 1935, cv, 761.
46. NYFELDT, A.: Klinische und experimentelle Untersuchungen über die Mononucleosis infectiosa, *Folia haemat.*, 1932, xlvii, 1.
47. ASH, H. H., and ARBOGAST, J. L.: Infectious mononucleosis, *Jr. Indiana Med. Assoc.*, 1942, xxxv, 562.
48. DE VRIES, S. I.: The icteric form of glandular fever, *Acta med. Scandinav.*, 1938, xcv, 552.
49. VAN BEEK, C., and HAEX, A. J. CH.: Aspiration-biopsy of the liver in mononucleosis infectiosa and in Besnier-Boeck-Schaumann's disease, *Acta med. Scandinav.*, 1943, cxiii, 125.
50. PRUEN, S. T.: Epidemic cervical adenitis with cardiac complications, *Brit. Med. Jr.*, 1914, ii, 21.

51. KIRKLAND, R.: Epidemic cervical adenitis with cardiac complications, *Brit. Med. Jr.*, 1914, i, 419.
52. DU BOIS, A.: De la pathogénie de l'angine à monocytes, *Acta med. Scandinav.*, 1930, lxxiii, 237.
53. BRADSHAW, R. W.: Mitral stenosis following infectious mononucleosis, *Ohio State Med. Jr.*, 1931, xxvii, 717.
54. (a) TILLET, W. S., and GARNER, R. L.: The fibrinolytic activity of hemolytic streptococci, *Jr. Exper. Med.*, 1933, lviii, 485.
- (b) TILLET, W. S., EDWARDS, L. B., and GARNER, R. L.: Fibrinolytic activity of hemolytic streptococci. The development of resistance to fibrinolysis following acute hemolytic streptococcus infections, *Jr. Clin. Invest.*, 1934, xiii, 47.
- (c) TILLET, W. S.: The occurrence of antifibrinolytic properties in the blood of patients with acute hemolytic streptococcus infections, *Jr. Clin. Invest.*, 1935, xiv, 276.
55. TIDY, H. L., and MORLEY, E. B.: Glandular fever, *Brit. Med. Jr.*, 1921, i, 452.
56. GOURICHON, H.: *Essai sur la fièvre ganglionnaire*, Thèse, Paris, 1895.
57. (a) CRAIG, H. R., and WHITE, P. D.: Etiology and symptoms of neurocirculatory asthenia. Analysis of 100 cases with comments on prognosis and treatment, *Arch. Int. Med.*, 1934, liii, 633.
- (b) GRAYBIEL, A., and WHITE, P. D.: Inversion of the T-wave in Lead I or Lead II of the electrocardiogram in young individuals with neurocirculatory asthenia, with thyrotoxicosis, in relation to certain infections, and following paroxysmal ventricular tachycardia, *Am. Heart Jr.*, 1935, x, 345.
- (c) DRY, T. J.: The irritable heart and its accompaniments, *Jr. Arkansas Med. Soc.*, 1938, xxiv, 12.
- (d) LOGUE, R. B., and HANSON, J. F.: Heart block. A study of 100 cases with prolonged P-R intervals, *Am. Jr. Med. Sci.*, 1944, ccvii, 765.
- (e) LOGUE, R. B., HANSON, J. F., and KNIGHT, W. A.: Electrocardiographic studies in neurocirculatory asthenia, *Am. Heart Jr.*, 1944, xxviii, 574.
58. (a) BRUENN, H. G.: The mechanism of impaired auriculoventricular conduction time in acute rheumatic fever, *Am. Heart Jr.*, 1937, xiii, 413.
- (b) ROBINSON, R. W.: Effect of atropine upon the prolongation of the P-R interval found in acute rheumatic fever and certain vagotonic persons, *Am. Heart Jr.*, 1945, xxix, 378.
59. CARTER, E. P., and DIEUAIDE, F. R.: Recurrent complete heart block with normal conduction between attacks, *Bull. Johns Hopkins Hosp.*, 1923, xxxiv, 401.
60. SADUSK, J. F., JR.: The skin eruption and false-positive Wassermann in infectious mononucleosis (glandular fever), *Internat. Clin.*, 1941, i, N.S. iv, 239.
61. LÖHE, H., and ROSENFELD, H.: Über Monozytenangina mit ausschliessendem vorübergehend seropositiven Erythema nodosum, zugleich ein Beitrag zur Differentialdiagnose zwischenluetischer und nichtluetischer Angina, *Dermat. Ztschr.*, 1928, liii, 373.
62. TIDY, H. L.: Glandular fever and infectious mononucleosis, *Lancet*, 1934, ii, 180 and 236.
63. WEBER, F. P.: Glandular fever and its lymphotropic blood picture—sometimes without obvious glandular enlargement, *Med. Press and Circ.*, N.S. cxxx, 65.
64. GOODING, S. E. F.: On glandular fever or infective mononucleosis, *Practitioner*, 1931, cxxvii, 468.
65. TEMPLETON, H. F., and SUTHERLAND, R. T.: The exanthem of acute mononucleosis, *Jr. Am. Med. Assoc.*, 1939, cxiii, 1215.
66. SADUSK, J. F., JR.: Temporarily positive Kahn and Wassermann reactions, *Jr. Am. Med. Assoc.*, 1939, cxii, 1682.
67. PRIEST, R.: Glandular fever, *Jr. Roy. Army Med. Corps*, 1935, lxxv, 159.
68. (a) JOHANSEN, A. H.: Serous meningitis and infectious mononucleosis, *Acta med. Scandinav.*, 1931, lxxvi, 269.
- (b) EPSTEIN, S. H., and DAMESHEK, W.: Involvement of the central nervous system in a case of glandular fever, *New England Jr. Med.*, 1931, ccv, 1238.

69. HUBER, W.: Beitrag zur Meningitis serosa bei Pfeiffer'schem Drüsenfieber, Schweiz. med. Wchnschr., 1938, lxxviii, 892.
70. (a) GSELL, O.: Meningitis serosa bei Pfeifferschem Drüsenfieber (Mononucleosis infectiosa), Deutsch. med. Wchnschr., 1937, lxxiii, 1759.
(b) SCHMIDT, V., and NYFELDT, A.: Infectious mononucleosis and meningoencephalitis, Ugesk. f. laeger, 1938, c, 336; as abst. Jr. Am. Med. Assoc., 1938, cx, 1884.
71. LANDIS, R., REICH, J. P., and PERLOW, S.: Central nervous system manifestations of infectious mononucleosis. Report of a case, Jr. Am. Med. Assoc., 1941, cxvi, 2482.
72. PAUL, J. R.: Infectious mononucleosis, Bull. New York Acad. Med., 1939, xv, 43.
73. FOORD, A. G., and BUTT, E. M.: The laboratory diagnosis of infectious mononucleosis, Am. Jr. Clin. Path., 1939, ix, 448.
74. (a) DOWNEY, H., and STASNEY, J.: Infectious mononucleosis. Part II. Hematologic studies, Jr. Am. Med. Assoc., 1935, cv, 764.
(b) DOWNEY, H., and STASNEY, J.: The pathology of the lymph nodes in infectious mononucleosis, Folia haemat., 1936, liv, 417.
(c) OSGOOD, E. E.: Fenestration of nuclei of lymphocytes: a new diagnostic sign in infectious mononucleosis, Proc. Soc. Exper. Biol. and Med., 1935, xxxiii, 218.
75. (a) DAVIDSOHN, I.: Heterophile antibodies in serum sickness, Jr. Immunol., 1929, xvi, 259.
(b) DAVIDSOHN, I.: Test for infectious mononucleosis, Am. Jr. Clin. Path., 1938, viii, 56.
(c) STUART, C. A., WELCH, H., CUNNINGHAM, J., and BURGESS, A. M.: Infectious mononucleosis, Arch. Int. Med., 1936, lvi, 512.
76. SOHIER, R., PARNET, J., and BERNIER, G.: Diagnostic sérologique de la mononucléose infectieuse par le test d'agglutination (réaction de Paul-Bunnell). Sa valeur pratique, Bull. et mém. Soc. méd. d. hôp. de Paris, 1939, lv, 846.
77. (a) WEBER, F. P., and BODE, O. B.: Beiträge zum "Drüsenfieber," München. med. Wchnschr., 1931, lxxviii, 1598.
(b) WAWERSIG, R.: Über unspezifisch-positiven Ausfall der Luesreaktionen im Serum bei der Monozytenangina, Med. Klin., 1937, xxxiii, 1737.
(c) BERNSTEIN, A.: False-positive Wassermann reactions in infectious mononucleosis, Am. Jr. Med. Sci., 1938, cxcvi, 79.
(d) HATZ, B.: The Wassermann reaction in infectious mononucleosis with report of a case with unusual clinical features, Am. Jr. Clin. Path., 1938, viii, 39.
(e) SAPHIR, W.: The Wassermann reaction in infectious mononucleosis, Am. Jr. Clin. Path., 1939, ix, 306.
(f) KAUFMAN, R. E.: False reactions for syphilis in infectious mononucleosis, Jr. Lab. and Clin. Med., 1941, xxvi, 1439.
(g) KOLMER, J. A., GINSBURG, I. W., and LYNCH, E. R.: The Wassermann reaction in infectious mononucleosis with special reference to the Kolmer test, Am. Jr. Clin. Path., 1942, xii, 316.
78. RADFORD, M., and ROLLESTON, J. D.: Two cases of glandular fever simulating typhus, Lancet, 1930, ii, 18.
79. DAVIS, B. D.: Biologic false positive serologic tests for syphilis, Medicine, 1944, xxiii, 359.
80. MILLS, J. H., and JAHN, E.: Negative serologic reaction for syphilis in nine patients with infectious mononucleosis, Jr. Lab. and Clin. Med., 1939, xxiv, 1076.
81. TURNER, T. B., and STERNBERG, T. H.: Management of venereal diseases in the army, Jr. Am. Med. Assoc., 1944, cxxiv, 133.

THE NUTRITIONAL STATUS OF JAPANESE PRISONERS OF WAR, BURMA 1945 *

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IN May 1945, during environmental and nutritional investigations on Indian soldiers in South East Asia, an opportunity offered itself for the study of 29 Japanese prisoners of war captured near Pegu, Burma, and held in a forward divisional prisoner of war cage.

It was thought that such a study would be useful as it might indicate what types of nutritional disturbance one could expect to find in Allied soldiers held captive by the Japanese in South East Asia, and their rehabilitation could be planned accordingly.

METHODS

Each Japanese prisoner of war was given a medical examination and stigmata of early nutritional failure, if present, were noted.

Blood and urine samples were collected from each prisoner of war and analyzed in a mobile biochemical laboratory. Blood hemoglobin, total protein and fasting serum vitamin C and serum chloride were measured, and urinary chloride, vitamin C, thiamine, riboflavin, and methyl nicotinamide were estimated. The methods employed and the mobile equipment used in these studies have been described in detail by Johnson et al.¹ The criteria employed in diagnosing nutritional deficiency² differ but slightly from those of Johnson and his colleagues.³

RESULTS

Medical Histories. When first seen the majority of the prisoners had been in the cage for three days and had eaten liberally of the food provided. They all consented to the examination and coöperated willingly. A Japanese interpreter was provided by Combined Services Detailed Interrogation Unit.

For three weeks previous to capture the majority of the prisoners had been living in the jungle on rice, rice and salt fish, or Burmese food. One had eaten nothing but mangoes during this time and another had been living on sugar cane. Both these men were very emaciated, and one had become pellagrous (see below).

Nine of the prisoners stated that during their service in Burma they had been treated in hospital for beriberi. One stated that, in August 1944, 80 per cent of his battalion who were north of Mandalay at the time, had come

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down with beriberi. It was also stated by another prisoner that because of the high rate of beriberi among the Japanese forces in Burma last year, all troops were ordered to take vitamin B₁ tablets every day.

However, of the 29 prisoners of war only five admitted that they had taken the tablets at all and only two had taken them regularly.

Physical Examination. Generally speaking there was little evidence of great weight loss. Three of the prisoners were emaciated, and about one quarter more had evidence of some recent weight loss. Many of them were covered with septic mosquito bites and thorn scratches. Fungus infections were negligible. A considerable number were obviously anemic. One had pellagra. He was emaciated, anemic, and had edema of his feet and ankles. His hemoglobin was 8.9 gm./100 ml. (40 per cent) and his serum protein,

TABLE I
The Biochemical Nutritional Status of Japanese Ps. O.W.

	Japanese Ps. O.W.	Indian Soldiers (2)	Canadian (6) and U. S. Army soldiers (1)
Hemoglobin	12.0	14.4	16.8
Gm./100 ml.			
Serum Protein	5.6	5.7	6.4
Gm./100 ml.			
Serum Chloride	98.1	100	105
Meq/L.			
Urine Chloride	0.7	0.5	0.7
Gm./hr. (fasting)			
Serum Vitamin C	0.1	0.13	0.8
Mg./100 ml.			
Urine Vitamin C	0.6	0.4	0.8
Mg./hr. (fasting)			
Urine Thiamine	9	13	13
Mcg/hr. (fasting)			
Urine Riboflavin	4	10	41
Mcg/hr. (fasting)			
Urine M. Nicotinamide	0.6	0.5	0.5
Mg./hr. (fasting)			

4.4 gm./100 ml. He had had watery diarrhea for three weeks and presented atypical pellagrous skin lesions of the type described by Field.⁴ Since he had been in the prisoner of war cage mild mental aberrations had developed.

Although none of the prisoners of war had skin lesions of vitamin A deficiency, six had chronic lesions of the eye with excess proliferative tissue and corneal scalloping or haziness, which probably dated from childhood. These lesions were much less marked than similar lesions which were very commonly seen among Indian soldiers, and which were considered to be signs of nutritional and environmental disturbances.⁵ The commonest lesions seen were cheilosis, angular stomatitis and invasion of the cornea, which are associated with riboflavin deficiency. The cheilosis and angular stomatitis were marked and were present in 13 (38 per cent) of the prisoners of war. Other lesions seen were glossitis (four prisoners of war) and edema (two prisoners of war).

The ankle reflex could not be elicited in three of the prisoners who stated that they had had beriberi, but no other clinical signs were discovered.

Biochemical Findings. The biochemical nutritional status of the prisoners of war as compared with the Indian soldier and North American soldier is shown in table 1.

From these figures it can be seen that major deficiencies in blood hemoglobin levels and in riboflavin output existed. Serum protein and vitamin C levels and urinary vitamin C and thiamine excretions were below par.

Further analysis showed that only six prisoners had a hemoglobin level which fell within normal limits and 17 had anemia (Hb. less than 80 per cent). Seven of the 17 had hemoglobin levels below 70 per cent of normal. Five prisoners had normal protein levels, while six had levels below 80 per cent of normal. The serum proteins of three others were below the edema level (4.5 gm./100 ml.). The urinary excretion of riboflavin was extremely low and four prisoners (14 per cent) did not excrete any riboflavin whatsoever.

COMMENTS

The low standard of nutrition found in the 29 Japanese prisoners of war is a reflection of the poor medical care given to the enemy in this theater of war. Although the number of men studied was not great, the results in part may be applicable to Japanese civilians and to Japanese forces in other theaters of operation.

The low hemoglobin and serum protein levels which were found are probably the result of malaria, poor dietary and hook-worm infestation. The thiamine levels were unexpectedly high especially when one considers that beriberi is not uncommonly seen in Japan and was certainly prevalent in Japanese soldiers fighting in the Burma theater of operations. Severe ariboflavinosis which was present, was probably the result of poor dietary intake. As yet we have not found any report in the literature of ariboflavinosis occurring in Japanese civilians or soldiers.

If the medical and nutritional care of the Japanese soldier has been as poor in other theaters of operation as it was in Burma, it is likely that considerable numbers of the enemy will require treatment for anemia, hypoproteinemia, and ariboflavinosis, as well as for other types of nutritional deficiency disease.

SUMMARY

1. Japanese prisoners of war captured in Burma in May 1945, presented clinical evidence of anemia, hypoproteinemia and ariboflavinosis.
2. Biochemical studies showed low levels of hemoglobin, serum protein, serum vitamin C and urinary riboflavin.
3. Serum and urinary chloride, and urinary methyl-nicotinamide and thiamine excretions were within normal limits.

BIBLIOGRAPHY

1. JOHNSON, R. E.: A field nutritional laboratory, War Med., 1945, vii, 222.
2. KARK, R. M.: The nutritional status of Indian soldiers, 14th Army. Report No. C6206 to the Associate Com. on Army Medical Research, N.R.C. Canada, 1945.
3. JOHNSON, R. E., SARGENT, F., ROBINSON, P. F., and CONSOLAZIO, F. C.: Assessment of nutritional and metabolic condition in the field. General and clinical aspects, War Med., 1945, vii, 227.
4. FIELD, H., JR., PARNALL, C., JR., and ROBINSON, W. O.: Pellagra in average population of Northern States, New England Jr. Med., 1940, ccxxiii, 307.
5. KARK, R. M.: Nutritional lesions of the eye in Indian soldiers. To be published.
6. KARK, R. M., and McCREARY, J. F.: The Prince Albert winter field ration trials, 1944, Edmond Cloutier, Ottawa, Canada.

BERIBERI IN JAPANESE PRISON CAMP *

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THESE observations on beriberi were made over a period of 34 months on approximately 8,000 Americans who had surrendered on Bataan and Corregidor. The 34-month period extended from April 9, 1942, with the surrender of Bataan, to January 30, 1945, with our release from captivity. We were handicapped by meager laboratory facilities, complete lack of co-operation of the Japanese officials, lack of supplies for records on these patients, inability to maintain follow-up records on the patients since they were moved in and out of the camp frequently, and also by the poor state of health of most of the medical officers. However, these obstructions to scientific study were over-compensated by abundance of clinical material. Hundreds of cases of any kind of vitamin deficiency disease were available for investigation at almost any time.

Beriberi was probably the most important vitamin deficiency disease encountered for several reasons. (1) Beriberi had the highest incidence, everyone in the camp having some form of beriberi at one time or another. (2) Beriberi had the highest morbidity. The disease was chronic in nature, incapacitating a soldier for months. (3) Beriberi had complications and sequelae, which were considered to be permanently disabling. (4) Beriberi was directly responsible for more deaths than any other vitamin deficiency disease.

The beriberi that was observed presented many novel features. It seemed far removed from the textbook picture.

APPEARANCE

Thiamine chloride deficiencies did not appear until late in the chronologic order of avitaminosis. A few cases of peroneal paresis and paralysis were seen in the first few months after capitulation. A maximum number of cases of peripheral neuritis appeared in January, 1943, after nine months of prison life. This was three to four months later than the appearance of manifestations of deficiency of the other vitamins in the B complex and about the same time as the onset of xerophthalmia, keratomalacia, and corneal ulcers from vitamin A deficiency. Scurvy was seen from time to time, but there were no large outbreaks. The chronologic order of appearance of all the vitamin deficiency diseases was carefully noted in hope of determining the storage capacities and the depletion periods of the body for the various vitamins. Of course, the appearance is also dependent upon the quantitative deficiency of each specific vitamin in the diet. Generally speaking, the diet was deficient in all vitamins. Also, the appearance depended upon the spe-

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cific pathogenesis. For example, in pellagra the mucous membranes and skin showed evidence of the disease almost as soon as deficiency occurred, but in beriberi degeneration of the nerves was slow and had progressed for several months before it became apparent. Therefore, we concluded that the late appearance of beriberi was not because of a large store of thiamine in the body, or because the diet was less deficient in thiamine chloride than in other vitamins, but rather because beriberi neuritis is a slowly progressive disease which appears several months after the provocative diet has been established. Actually, the store of vitamin B is less than that of other vitamins. The depletion period is usually stated to be from seven to 18 days on an entirely deficient diet.¹ The onset at times was hastened when the patient suffered from malaria or dysentery. Symptoms frequently were first noted after a malarial chill. This was not peculiar to beriberi. Pellagrous lesions were commonly seen in 24 to 48 hours after a malarial chill.

DIET

Beriberi was a natural consequence of our deficient diet. The diet varied from time to time but, roughly speaking, it was bad during 1942, improved during 1943, and was bad again in 1944. The diet issued by the Japanese was augmented occasionally by food purchased from the commissary, from the underground, from our own gardens, by what could be stolen from the farms, and by two shipments of Red Cross food. The total caloric value of the diet varied from about 900 to about 2,000 calories. The main staple was rice, but at times corn, camodies, casava and gabi were substituted for a portion of the rice. Vegetables, the leafy portions, fresh carabao meat, fish, oil, sugar and small amounts of fresh fruit were also issued. The diet was never considered adequate for vitamin B requirements. The rice that was issued was of medium mill. The pericarp which contains vitamin B was about half removed in the process. Adding the thiamine contained in this to the small amount in the leafy portion of the vegetables, and in an occasional dab of fresh meat, there was still a wide gap between this sum and the minimum physiologic requirements of 1.8 mg. per day.² Of course, this figure varies with caloric intake and the ratio of fat to carbohydrate in the diet. The thiamine chloride deficiency was exaggerated by the high carbohydrate and low fat content of the diet provided. It was the worst possible diet for one trying to sustain health on a low thiamine intake, since carbohydrates require more thiamine for their metabolism than either fat or protein, and also because fats have a thiamine-sparing action.³ Attacks of diarrhea, vomiting, and malarial chills also increased the requirement. Consequently the incidence of beriberi was tremendous. Over 75 per cent, or 5,000 to 6,000 men at one time had painful neuritic feet.

WET BERIBERI

Two types of beriberi are considered, wet and dry. So-called acute beriberi is just one type of beriberi heart disease in which acute cardiac failure

is the salient feature. True wet beriberi is manifested by dependent edema due to deficiency of thiamine chloride. The exact mechanism involved in the formation of the edema is not known. Presumably it is not an edema of cardiac origin. The plasma proteins in these patients should be normal or at least above the critical edema level of 5.5 gm. per 100 c.c. of plasma.⁴ Theoretically, thiamine chloride should precipitate a diuresis and cause the disappearance of the edema. This consideration is academic, since usually a diet that is sufficiently deficient to result in beriberi will also be low in protein. It is doubtful that we saw any true wet beriberi in our camp. The edema which appeared even in the days of fighting in Bataan, and through the entire prison life, was not dependent upon a thiamine chloride deficiency per se, for it appeared three to four months before the onset of polyneuritis. The diet had been low in protein content, and it is probable that the plasma proteins were below the critical edema level. Both hypoproteinemia and thiamine chloride deficiency were undoubtedly present in every edematous patient after a few months on the prison diet. Thiamine chloride alone, however, was unsatisfactory in treatment except in a few early cases, in which it seemed to precipitate a diuresis which may have been coincidental. It might be assumed that these patients probably had plasma proteins above the edema level and that thiamine chloride might have been necessary to establish a normal water metabolism. Later it had no effect on thousands of cases of edema. On the other hand, an increased protein intake for just a few days would improve the water balance. If a patient was developing edema during the day and having a nocturnal frequency of urination of 10 to 12 times a night, the ingestion of a small amount of protein would decrease the frequency by at least half. Increased plasma protein and increased osmotic pressure of the blood plasma prevented escape of fluid into the tissues during the day, thereby decreasing nocturia. On the other hand, a patient with manifest and persistent edema would have a diuresis after ingestion of small amounts of protein. These changes in water balance were noted after eating only an 8 to 12 ounce can of fish (about 90 gm. of protein). We concluded that the edema was dependent upon a low protein intake and hypoproteinemia, not upon a wet beriberi. This does not preclude the existence of wet beriberi, but in these patients thiamine did not correct the water imbalance.

The edema was dependent in nature. The ankles were swollen at the end of the day and the face was swollen in the morning. Severity varied from subclinical or slight pitting to anasarca with fluid in all serous cavities. Everyone in the camp had some degree of edema at some time. The maximum number occurred in the first eight months, and particularly just after "the death march." The edema was worse at that time because of an orthostatic factor, since the men had been on their feet for days on a forced march. There was an improvement after arrival of the Red Cross packages in Christmas of 1942. There was then no change until late in 1943 when edema reappeared, but it improved with the second Red Cross shipment of

food in the Christmas of 1943. There was a steady increase in number of nutritional edema patients by 1944, until by January, 1945, about 40 per cent of those in the camp were so afflicted. The total protein content of the diet during the two bad years, 1942 and 1944, was calculated to be less than 30 gm. per man per day. Of this, 20 gm. were vegetable protein. We lived on 6 to 8 gm. of animal protein per man per day for over one year. This was once considered to be a physiologic impossibility. We admit our state of health was poor, but we managed to sustain life on this low protein diet. Beriberi heart disease, another etiologic basis for edema in a few patients, will be discussed later.

The course of the edema was entirely dependent upon protein intake. Usually edema did not inconvenience the patient, but a few required removal of fluid from the pleural cavities. Patients complained of heaviness of the feet and inability to get their feet into their shoes. There were no deaths from nutritional edema. The swelling did contribute to poor nutrition of the skin, which at times would macerate and weep, forming a large chronic ulcer.

The treatment consisted of extra protein feeding. The Japanese issued 10 cans of evaporated milk per day for the entire hospital, which at times had to be divided between 2,100 or 2,200 men. This futile gesture had no real effect. Mongo beans, peanuts, canned fish, and beef from the commissary and later Red Cross food were issued to the worst cases. Sometimes the results were dramatic, a patient losing from 50 to 75 pounds of edema in a few days. This was true also after intravenous administration of a few bottles of plasma. A salt-free diet was recommended but was difficult to enforce since it was extremely difficult to eat plain unseasoned rice and whistle-weed soup. At other times salty fish was the only source of protein, but the patient was encouraged to eat it regardless of the salt content. Fluids were curtailed because salt restriction could not be enforced. Diuretics, namely salyrgan and caffeine, were successful at times. Their effect was enhanced after intravenous use of plasma. Thiamine chloride had no effect on the water balance. Mechanical removal of the fluid was necessary at times. Occasionally the edematous fluid was evacuated via the bowel.

DRY BERIBERI

Dry beriberi was almost always characterized by sensory symptoms of a symmetrical, ascending, peripheral neuritis. Motor disturbances were mild except in a few patients who developed foot or wrist drop. Painful feet or hands were predominant complaints. Motor and sensory symptoms did not usually exist in the same patient. Peroneal or radial nerve paresis or paralysis usually developed suddenly without going through the painful stage. Rarely did a patient progress from a painful state to motor paralysis, and when this occurred the pain would stop owing to development of a complete

anesthesia. Strangely enough, few men, less than 2 per cent in the entire camp's history, developed motor paralysis, whereas over 75 per cent had predominately sensory disturbances or painful feet. Other manifestations of dry beriberi were attributable to spinal cord lesions, apparently of the posterolateral tract; intra-ocular optic neuritis with gradual diminution of vision and optic atrophy; "beriberi spots," a skin lesion similar to erythema nodosum; and finally beriberi heart disease. Psychosis, breast tumors,* and transitory arterial hypertension were also seen, but a causal relationship was not established.

The first symptoms of a peripheral neuritis were stiffness, heaviness, or a tired feeling in the arches of the feet. At first we attributed this to going barefoot or wearing a homemade wooden clog. Soon there was aching in the arch and soles of the feet. This progressed to a dull, throbbing, deep bone ache in the whole foot. Soon sharp, shooting pain appeared, radiating from the arch to the tip of the toes. Burning pain, especially on the soles of the feet, paresthesia, and extreme tenderness next developed. These symptoms increased in severity until the patient was "half crazy." There was no relief. He would rub his feet or just look at them and cry. A common practice was for patients to sleep side by side, with heads in opposite directions, so that each could rub the other's feet. Soaking in water was a frequent, but not too successful remedy. Some unfortunate victims were unable to sleep, and their nights were spent in crying, moaning, and begging for relief. The pain soon spread up the legs to the knees, occasionally to the hips and a few even had pains and paresthesia across the abdomen, chest and scalp. After the feet were severely involved, pain developed in the fingers. Rarely did the symptoms advance above the elbows. In severe cases of long duration, the patient complained that the extremities were going to sleep or were dead. This anesthesia afforded some relief. The pain was worse during the daytime. It seemed to progress during the heat of the day and to improve with the coolness of the night or after a shower. The formation of edema in the legs eased the pain probably by a pressure anesthesia.

Complaints of a systemic character were insomnia, nervousness, anorexia, fatigability, palpitation, shortness of breath on exertion, and emotional instability, appearing simultaneously with the local symptoms. Gastrointestinal symptoms such as distention, excessive gas, foul breath and aerophagia were common complaints, but could not be evaluated because of the presence of many other possible causes such as dysentery, pellagra, worms and other intestinal infections.

Physical examination of such a patient revealed a thin, emaciated, malnourished male, weighing on an average 100 to 110 pounds. He was nervous, jumpy, and obviously suffering from acute pain. Examination of the affected parts revealed a mottled, erythematous skin. The soles of the feet and palms of the hands were often fiery red, an excellent picture of so-

* To be reported elsewhere.

called palmar erythema. Excessive sweating was noticed. Pronounced dermatographia was another sign of vasomotor disturbance. Occasionally the finger nails had disappeared or showed transverse grooves, usually two or three, while between them there was apparently normal nail. These grooves were the result of a period of small rations, and the normal nail of a period when the rations were better. We were reminded of the rings of a tree, corresponding to droughts and rainy seasons. There was a stocking and glove distribution of the sensory disturbance, usually to the level of mid-forearm and mid-thigh. Areas of paresthesia, hyperesthesia, pallanesthesia, hypesthesia, and anesthesia were found in the same extremities. Deep and superficial tenderness was severe. If we attempted to grab the patient's feet, he would jump and shriek as in mortal terror. Muscle tenderness was usually present but not severe. Muscle strength was very little changed. All patients were able to stand from a squatting position. At first the deep tendon reflexes were normal. At the height of the disease, about 40 per cent had 1 plus to 2 plus exaggeration of the deep tendon reflexes. No other abnormal reflexes were noted except in the groups which demonstrated spinal cord lesions or true paralysis. The gait was so unique, it was called the "Cabanatuan shuffle." It was protective because of the tenderness of the feet. The weight was placed on the outer side of the foot; each step was slow and deliberate; the patient looked carefully for a smooth place, then he gingerly placed his foot down, flinging his arms upward. Were it not for the suffering that it portrayed, it would have been a most amusing sight to see hundreds of men thus hopping across the compound.

Among this large group of patients with peripheral neuritis, about 50 per cent had visual complaints. Of this group, about 10 per cent had severe diminution of vision. These complaints appeared concomitantly with the development of severe neuritis and were distinct from the symptoms of xerophthalmia, keratomalacia, and corneal ulceration. It was simply a matter of inability to see with the usual clarity. Examination of the eyes demonstrated a gradually failing vision. Previously the visual acuity had been 20/20 or near normal. The loss was slow until 10 per cent, or about 500 men, had a vision of 20/200 or less. There was a narrowing of the visual fields and an enlarged blind spot. At first fundoscopic examination revealed a blurring of the disk margin. After two or three months there was more visual disability and a temporal pallor and macular degeneration. The height of the disability was reached after four to five months. The nerve head was white and a high grade optic atrophy had resulted. This process was considered to be an intraocular optic neuritis due to beriberi. There was no demonstrable loss of auditory acuity.

Another lesion, which was commonly seen in the patients with peripheral neuritis, was a skin lesion resembling erythema nodosum. This lesion was called "beriberi spots." We assumed that it was due to deficiency of thiamine chloride, but we were not at all certain of this. These spots were seen in hundreds of patients with peripheral neuritis. Their appearance co-

incided with the onset of the neuritic symptoms. The lesion was intracutaneous or subcutaneous. The site of predilection was the shin. It was symmetrical, slightly elevated, hot, tender and pink, extending over an area usually one inch to two inches in diameter. At times the lesions were fairly well circumscribed, appearing as an erythema nodosum. Again they were not circumscribed and appeared as a subcutaneous cellulitis. The lesions ran a rapid course, reaching their height in intensity in 24 hours. At times their appearance was preceded by a chill. Fever from 99° to 102 or 103° was usually present. The lesion was self-limited, resolving in 72 hours. Desquamation and brownish pigmentation of the skin followed resolution. There were no complications, except in a few cases where there was supuration of the lesion. They were recurrent in nature; a man might have them every month to six weeks, almost in the same place, usually the shins. They disappeared as the peripheral neuritis improved. Although these patients certainly had a polyavitaminosis, the predominant nutritional disease at that time was beriberi. Therapeutic tests with ascorbic acid, niacin, and thiamine chloride were inconclusive. Even sulfanilamide was tried because of the inflammatory appearance. Most of us agreed that the "spots" disappeared as quickly with no treatment as with any of the drugs that were available. From our clinical observation, we concluded that "beriberi spots" were probably due to a thiamine deficiency even though therapeutic tests were not convincing.

A small number of patients, estimated to be 25, demonstrated involvement of the spinal cord. Here again, the etiology of the lesion was not clear. Although definite proof is lacking, clinically it was closely associated in appearance and course with beriberi. These patients usually showed a spastic paraplegia and more rarely a spastic quadriplegia. The onset was usually slow, taking a week or two, but at times was abrupt. These patients had a positive Romberg test, uncertain and ataxic gait, and positive Babinski reflexes. The sensory disturbances of peripheral neuritis were also present but were not necessarily maximum in degree. Attempts to discover some cause other than vitamin deficiency disease were unsuccessful. We concluded that the ataxia and lack of coördination were not dependent on the loss of sensory impulses but due to involvement of posterolateral columns of the spinal cord, probably resulting from beriberi.

BERIBERI HEART DISEASE

Cardiovascular manifestations were encountered in the majority of patients with beriberi, but were extremely difficult to evaluate. The criteria for diagnosis of beriberi heart disease were (1) signs and symptoms of peripheral neuritis, and (2) symptoms referable to the heart without any other demonstrable cause. The criteria of dietary inadequacy are not listed because all men were suffering from malnutrition and were good candidates for any kind of vitamin deficiency disease. Also, a therapeutic test with

thiamine chloride would have been extremely valuable in establishing the diagnosis in these patients, but unfortunately our supply was so limited that this was denied to us. Consequently, the diagnosis was controversial at times. Undoubtedly it was diagnosed too frequently since there were meager laboratory facilities with which to discover other possible causes for the heart disease. These manifestations did not necessarily occur in the severest cases and usually no edema was present. All were of military age except for a few older civilians. Enlargement of the heart, either of the right side or left side, was not considered necessary for the diagnosis of beriberi heart disease. Extremely difficult was the differentiation of neuro-circulatory asthenia and beriberi heart disease. Several well known neurotic patients developed beriberi and began to have cardiac complaints such as palpitation and dyspnea on exertion. The differentiation was almost impossible without an electrocardiogram and an adequate therapeutic test. We had nothing more than advice to offer these patients, but it was questionable whether to advise them to stay in or to get out of their beds.

The symptoms varied from dyspnea, palpitation, irregularities of the heart beat, and sudden attacks of pounding of the heart to the symptoms of congestive heart failure with orthopnea and prostration. Seldom was there complaint of precordial distress.

Examination of these patients revealed the heart to be usually of normal size. More than a hundred roentgenograms of the cardiac shadow failed to reveal any cardiac enlargement. The heart was usually hyperactive. A precordial pulsation was noted. The rate was from 130 to 140. Irregularities of the rhythm were frequently found, premature beats or extrasystoles, dropped beats, attacks of paroxysmal auricular tachycardia, and rarely a bradycardia of 30 to 40 per minute. In one group of 60 men that I observed, six had repeated attacks of paroxysmal auricular tachycardia. Almost every kind of arrhythmia was suspected, but without an electrocardiogram they could not be positively identified. Frequently a soft systolic murmur was heard over the precordium. At times a third heart sound was heard and a bifid apex impulse beat could be felt. Blood pressure was slightly lower than normal, ranging from 100 mm. Hg systolic and 60 mm. diastolic to 80 mm. Hg systolic and 40 mm. diastolic. Usually there was no evidence of decompensation. These were the findings in over 95 per cent of patients diagnosed as beriberi heart disease.

The second type of beriberi heart disease ran a chronic course, with enlargement of the cardiac shadow usually of the right side, and with cyanosis, hepatomegaly, râles in the bases of the lungs, dyspnea, dependent edema, and a fast, thready pulse. Only 20 to 25 patients were included in this group. The diagnosis was chronic beriberi heart disease with both left and right ventricular failure. Most of these patients died within a year without receiving adequate treatment. One patient who had been decompensated for about six months was finally given 10 mg. of thiamine chloride every day. Despite this the patient died. Autopsy revealed an enlarged

heart estimated to be about 500 grams. There was a dilatation and hypertrophy of both the left and right ventricle, but much more on the right. The auricles were slightly dilated. There was a large organized thrombus attached to the wall of the right ventricle, about 2 by 3 cm. This was the result of the long-standing decompensation, dilatation of the heart, and sluggish circulation. It was obvious why thiamine chloride did not help this patient. Digitalis was tried in most of these patients but, as expected, seemed to have no effect on the decompensation.

The third type of beriberi heart disease manifested itself in acute dilatation of the heart, pulmonary edema, and death within a few minutes to 24 to 48 hours. These patients had peripheral neuritis and usually no edema. They occasionally had symptoms referable to the heart, such as palpitation or poor exercise tolerance. One minute prior to the onset they were walking around and the next minute they collapsed. We felt that exercise was extremely dangerous to patients with peripheral neuritis since their hearts were already weakened. Acute cardiac death occurred in young as well as middle-aged men. The estimated number of these deaths was 50; undoubtedly, the figure would have been higher if painful feet had not prevented them from walking.

Beriberi heart disease was manifest in three ways: (1) Normal size heart with arrhythmias and decreased tolerance to exercise. (2) Enlarged heart with chronic left and right ventricular failure. (3) Acute cardiac dilatation, pulmonary edema and death.

Conclusions: (1) Enlargement of the heart is not to be expected in the majority of cases of beriberi heart disease. (2) Thiamine deficiency may be the cause of almost any type of cardiac arrhythmia. (3) Both left and right ventricles are involved in congestive heart failure in beriberi heart disease. (4) Digitalis is without benefit in the treatment of beriberi heart failure. (5) Beriberi heart disease is an acute medical emergency which must be treated energetically to prevent secondary irreversible damage or death.

COURSE

The course of beriberi patients depended upon the severity of the lesions and complications. Except for the deaths of the patients with cardiac manifestations they continued to live although severely incapacitated at times. There were exacerbations of the symptoms during the low ration period and improvement with a better diet. It was as long as four to six weeks between the increase in ration and improvement in symptoms. After several years the patient seemed to have accustomed himself to a lower vitamin B₁ intake.⁵ Another explanation was that thiamine chloride was synthesized in the gastrointestinal tract after a period of time. Despite this, about 15 per cent of the men complained of hyperesthesia, aching of the feet, deep and superficial tenderness even at the time of release in January, 1945. The common sequelae were optic atrophy, a few cases of spinal cord lesions, muscular atrophy, paralysis of leg muscles, and sensitivity of the feet.

DIAGNOSIS

The diagnosis of beriberi was obvious after the first symptoms had been evaluated. A typical peripheral neuritis was present, i.e., ascending and symmetrical. Almost all the complaints were of a sensory nature. We could not explain why these patients did not show more signs of motor involvement. Orthopedic causes, metabolic neuritides, and vascular disease were ruled out. The etiology was based on one common denominator, vitamin deficiency disease. Thiamine chloride deficiency was probably the cause for the manifestations that have been discussed, although there is a good deal of question about the beriberi spots and the spinal cord lesions.

TREATMENT

Little can be said of the treatment of these patients in our camp. The minimum therapeutic dose of 20 mg. of thiamine chloride per day was rarely available for the patients. For over a year 1 to 2 mg. per day was the standard dose. Many times there was no synthetic thiamine available. After the Red Cross supply of 1943 arrived, there was a sufficient amount to give 10 to 20 mg. and occasionally over 20 mg. per patient per day for a 10-day course. By that time most of the men were cured or markedly improved by the increased diet. Exceptions to this were the patients with foot drop who showed almost no improvement despite the administration of 20 mg. of thiamine per day for six months or longer. In the early days we used a yeast culture made from rice, sugar, and brewer's yeast. Each man received from 6 to 8 ounces a day of this preparation. Calculating from the yeast cell count each patient received about 3 mg. of thiamine chloride per day from this source. Small amounts of rice polishing, tiki-tiki, and brewer's yeast were available. Extra foods were shunted to these men. Actually, Red Cross foods and the special meat issue were paramount in the improvement and cure of these patients. Quinine had a deadening effect on the pain in the extremities. That drug also was so scarce it had to be given only for malarial chills and fever. Narcotics were conscientiously withheld but it was difficult to keep from giving morphine to a friend who was crying from acute agony.

SPECIAL STUDY

There was only one small group of Americans who were adequately treated during the acute illness. This was a group selected for study by a Japanese doctor. A board of seven American doctors conducted the study under the surveillance of the Japs. It was a therapeutic response experiment. It was far removed from a scientific study; however, the patients benefited from the extra vitamins that were made available. Ninety-six of the severest cases of painful feet were selected for this study. They all demonstrated the typical "Cabanatuan shuffle" and sensory manifestations of symmetrical ascending peripheral neuritis of beriberi. It has been stated previ-

ously the typical lesion was a sensory disturbance with usually little to no involvement of the muscular strength. No patients with cord degenerative lesions, muscular paralysis, active malaria, or dysentery were included. Complete physical and neurologic examinations were made on all patients and recorded. Blood count showed routinely a secondary hypochromic anemia and leukopenia of from 3,000 to 5,000. The urine was normal. Roentgenograms of the long bones showed 1 plus to 3 plus osteoporosis. This was still present three to four months after our liberation. This raised the question whether vitamin deficiency disease plays a rôle in the process of osteoporosis. It may tend to exaggerate the imbalance of calcium-phosphorus in a deficient diet. Six foot roentgenograms of the chest revealed a heart shadow of normal size. Despite this finding almost every man complained of dyspnea and palpitation and occasional attacks of paroxysmal auricular tachycardia. Fractional gastric analyses showed usually no free hydrochloric acid in the fasting specimen and low hydrochloric acid in the others. Spinal fluid on these patients was normal as to dynamics and cytology. Increased spinal fluid pressure is sometimes given as a diagnostic aid in beriberi but was not a finding in our patients. Ophthalmoscopic examination revealed an optic atrophy in a majority of the patients. Visual acuity was usually less than 20/200. In a few patients blood chemical tests were made by Japanese technicians but were never reported to our board.

There were eight groups of 12 men each. Each group was treated differently as listed below. The medication was given for a three-week period. The dosage shown is the daily dose per man.

Group I (a) 6 men	10 mg. thiamine chloride intrathecally
	10 mg. thiamine chloride subcutaneously
(b) 6 men	20 mg. thiamine chloride subcutaneously
Group II	60 gm. powdered brewer's yeast
	10 mg. thiamine chloride subcutaneously
Group III (completely treated)	1 c.c. liver extract intramuscularly
	20 mg. thiamine chloride subcutaneously
	60 gm. brewer's yeast
	1 c.c. liver extract intramuscularly
	250 mg. niacin
	200 mg. ascorbic acid subcutaneously
	1 c.c. B complex preparation subcutaneously
	60 c.c. cod liver oil orally
	4.5 mg. riboflavin orally
Group IV	1 gm. calcium phosphate orally
	60 c.c. cod liver oil orally
Group V	1 gm. calcium phosphate orally
Group VI	200 mg. ascorbic acid subcutaneously
Group VII	250 mg. niacin subcutaneously
Group VIII	4.5 mg. riboflavin orally
	Control. This group received placebos.

All of these patients were issued the same diet. The diet at that time consisted approximately of 20 gm. of animal protein, 350 gm. of rice, a 3 ounce serving of cooked mongo beans and varying amounts of vegetables, 10 gm. of sugar, some oil and occasionally bananas and limes. The caloric value was approximately 1600. The patients were needlessly advised to eat all the ration and nothing else.

The patients were examined and questioned every day for the first month. The results were recorded as to severity from zero to 4 plus. A schematic drawing was kept on each patient indicating the areas of anesthesia, hyperesthesia, paresthesia, and degree of tenderness, reflexes, strength, and appetite. After the first two months, examinations were made every week; the observation period lasted for a total of five months.

Despite our high hopes and enthusiasm we were unable to find any startling results. There were no clear-cut differences in the amount of improvement in the first two months. All the groups, and even those not included in our study, showed the same amount of improvement during this period. Soon afterward, however, the patients in groups I, II, III, or those receiving thiamine chloride or B complex, showed an improvement of the appetite, less insomnia, less irritability, and more emotional stability. The pulse rate dropped from around 130 to 140 down to 90 to 100. Exercise tolerance improved. Less tremor of the hands and feet was noted. There was no perceptible change in the pain in the hands and feet at this time. However, some men who had progressed to the stage of anesthesia of the extremities complained that they were "waking up." This proved to be a common finding. Thiamine chloride seemed to cause an increase in the pain before improvement set in. Dyspnea, palpitation and arrhythmias of the heart were other findings which showed an early improvement. It was not until four months that group III, or the completely treated group, evidenced slightly more improvement in the sensory manifestations; this consisted of less pain and tenderness in the extremities. The sweating, dermatographia, plantar and palmar erythema were lessened. The optic nerve lesions and visual acuity were not changed by the treatment. Group II, B complex, was next in the amount of improvement. Group I patients received thiamine chloride alone and showed no more improvement of the pain in the extremities than the control group. There was no choice to be had in the remaining groups. All showed a gradual improvement similar to that shown in the entire camp.

Conclusive results were not obtained because the patients were still issued a border-line starvation diet. The dosages and length of treatment were inadequate. The neuritis had persisted for about six months prior to the time of treatment. Extensive nerve damage had been done; consequently the repair was slow. However, we hoped that a temporary saturation of the patient with thiamine chloride had been reached in the treatment of the first three groups. One man from group III, the completely treated group, clarified this point for us. On the day following the end of three weeks' treatment, he had a malarial chill and fever; the next day pellagrous lesions, hemorrhagic blebs, appeared on both legs. Within two days he had a complete bilateral peroneal paralysis. With the appearance of the motor disturbance, his sensory complaints ~~quickly disappeared~~. The pellagrous lesions soon responded, but the foot drop persisted for over a year and a half despite specific therapy.

CONCLUSIONS

1. Thiamine chloride first corrected the anorexia, nervous manifestations, tachycardia, arrhythmia, and improved the exercise tolerance of the heart in patients with beriberi.
2. Beriberi peripheral neuritis responded sooner to the entire B complex than to thiamine chloride alone.
3. Intrathecal route of administration was no more efficacious than subcutaneous injection.
4. Complete saturation of the body with thiamine chloride was not attained by a short course of large doses.
5. More vitamins can still be bought in a grocery store than in a drug store.
6. There may be nutritional causes of polyneuritis other than lack of thiamine.
7. Palmar and plantar erythema are consistently seen in dry beriberi.
8. "Beriberi spots" is a newly described skin lesion probably due to thiamine deficiency.
9. Motor manifestations are often minimal or lacking in beriberi peripheral neuritis.
10. Posterolateral column degeneration of spinal cord in malnutrition is probably due to lack of vitamin B₁.
11. An irreversible optic atrophy may result in severe beriberi.

BIBLIOGRAPHY

1. HULSE, M. C., and others: Subclinical vitamin deficiency; assay of subclinical thiamin deficiency, *Ann. Int. Med.*, 1944, xxi, 440-446.
2. Committee on Food and Nutrition, National Research Council: Recommended daily allowances for specific nutrients, *Jr. Am. Med. Assoc.*, 1941, cxvi, 2601.
3. ELVEHJEM, C. A.: Handbook of nutrition; water soluble vitamins, *Jr. Am. Med. Assoc.*, 1942, 1388-1397.
4. MOORE, N. S., and VAN SLYKE, D. D.: Relationships between plasma specific gravity, plasma protein content and edema in nephritis, *Jr. Clin. Invest.*, 1930, viii, 337-355.
5. MEYERS, F. M.: Possible adaptation to low vitamin B₁ intake, *Am. Jr. Med. Sci.*, 1941, cci, 785-789.

SUDDEN DEATH IN RHEUMATIC FEVER *

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INTRODUCTION

ABRUPT cessation of heart beat, as distinguished from gradual failure, involves mechanisms of which we know little.^{1,2} Sudden death occurring in this manner often finds no adequate pathologic explanation, although there is usually evidence of cardiac and aortic disease. In searching for a plausible general hypothesis, that of acute circulatory impairment in the heart, lungs, or brain-stem appears not unattractive. Although vascular occlusion by emboli, by thrombi forming in damaged areas, or by gradually progressing sclerosis has long engaged the attention of pathologists, awareness of functional vascular changes, in part, perhaps, referable to the autonomic nervous system³ of acute "hyaline" thrombosis, and of acute lesions in arterial walls is more recent. Such changes have been studied experimentally in anaphylaxis and related phenomena, and it is noteworthy that acute arterial lesions may be difficult to distinguish from those designated as arteriosclerosis. Rich and Gregory have presented evidence suggestive of a close parallelism between the pattern of "rheumatic fever" and that of anaphylactic hypersensitivity. We have recently reported pathologic findings which accord well with that hypothesis. One might, therefore, expect to find instances of sudden death in rheumatic fever. Although the literature contains little on this topic, it is the considered clinical opinion of one of us that such occurrences are more frequent than is generally realized. It seemed desirable, therefore, to report three cases of sudden death in patients at the rheumatic fever unit of this hospital.

SOURCE OF THE MATERIAL

The Rheumatic Fever Unit of the U. S. Naval Hospital, Corona, California, is the source of the material contained in this report. From a case-load of 7165 rheumatic fever patients observed over a period of 18 months, 13 deaths occurred. Three of the 13 deaths occurred suddenly and dramatically. The three cases of sudden death occurring in the course of very mild rheumatic fever are the basis of this presentation.

CASE REPORTS AND PATHOLOGICAL FINDINGS

Case 1. J. C., a 28 year old male of medium height and sthenic build, was admitted to the sick list November 10, 1943, complaining of painful and swollen knee joints. There was no history of a previous attack of rheumatic fever. He had an

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From the Rheumatic Fever Unit, U. S. Naval Hospital, Corona, California.

attack of tonsillitis three weeks previous to the onset of the painful joints. Examination revealed very slight fever, migrating joint involvement and an elevated blood sedimentation rate. With bed rest and salicylate therapy he improved. He continued upon treatment with rest and mild bed exercises. On January 20, 1944, physical examination was essentially negative. He complained of mild joint pain unaccompanied by swelling or tenderness. At that time the blood sedimentation rate was 45 mm. per hr. (Westergren). The electrocardiograms were normal, except for an inverted T_3 wave. There was no Q_3 wave present (figure 1). He was treated with

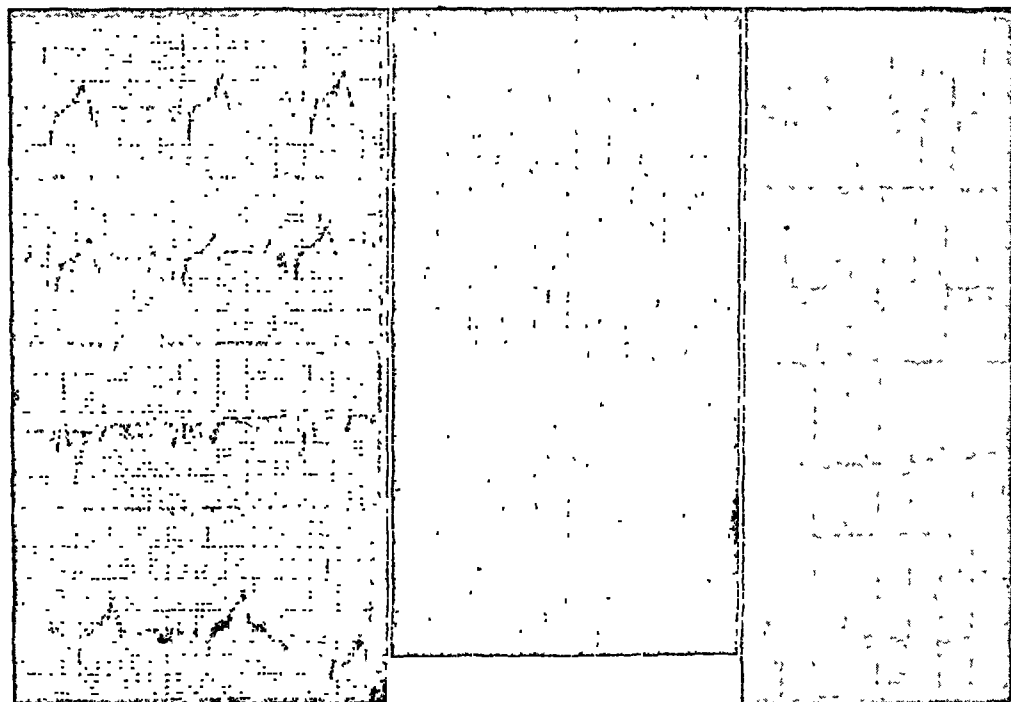


FIG. 1.

FIG. 2.

FIG. 3.

bed rest and salicylates and a gradually increased program of activity for a period of nine months. During the eighth and ninth months physical activity was increased until he could do light ward duty for four hours daily without symptoms. In the seventh month of illness a faint apical systolic murmur was heard in the recumbent position only. In the ninth month when no signs of rheumatic activity persisted, except a blood sedimentation level of 15 to 20 mm. per hour (Cutler), it was felt wise to remove badly diseased tonsils. The patient was prepared for tonsillectomy by giving 25 grains of sodium salicylate combined with 10 grains of sodium bicarbonate every four hours for one week, and 15 grains of sulfathiazole t.i.d. for two days prior to operation. Preoperative medication consisted of nembutal, gr. $1\frac{1}{2}$ and atropine sulfate, gr. $1/150$. Under novocaine local anesthesia tonsillectomy was performed without difficulty and without any change in the patient's circulatory state. The patient walked from the operating chair to a wheel-chair, and was put to bed upon the ward. Patient looked well and felt well. Suddenly, one hour later, the patient became pale, then cyanotic and was found to be pulseless. No heart beat was audible. Respirations continued for several minutes longer. Efforts at resuscitation were futile.

Gross pathologic examination showed the following noteworthy findings: There was marked cyanosis of lips and nail-beds. Upon examination of the thoracic contents, the heart was found to measure transversely 17.0 cm., and the internal diameter

of the chest 30.0 cm. The pericardium was moderately thickened and contained a few c.c. of blood-stained fluid. The heart weighed 540 gm. There were numerous small subepicardial hemorrhages. The circumference of the tricuspid orifice was 11.0 cm., of the mitral orifice 11.0 cm. The tricuspid and mitral leaflets showed streaky thickening. One mitral cusp was markedly retracted. There were what appeared to be calcified plaques on the aortic cusps. The base of the aorta was greatly thickened. There was gross distortion and narrowing of the right coronary ostium. Both coronary arteries and the main branches were grossly thickened and the lumen appeared almost entirely occluded. The lungs showed marked congestion in some areas, while other areas appeared relatively bloodless. There was no obstruction in the bronchial tree or in the main pulmonary arteries.

The microscopic findings of interest were, first, accumulation of relatively homogeneous extracellular material in the coronary arteries and at the base of the aorta. Masson stains showed this material to be largely neutrophilic, though intensely acidophilic (fibrinoid?) areas were present. Elastic tissue stain of a coronary artery showed that this material was largely intramural. Aggregates of large Aschoff-like cells were noted in some areas, and there was endothelial proliferation in others. Endothelium-lined spaces were present, and were probably new vascular channels. Small coronary branches showed marked cellular proliferation. The valvular and mural endocardium showed accumulation of hyaline material similar to that in the arteries. Collections of "Anitschow myocytes" were scattered throughout the myocardium. Similar cells were conspicuous at the base of the aortic cusps. A lung section showed an artery occluded by material similar to that seen in the coronary arteries, but containing more cells and evidence of organization, and the appearance of the surrounding lung was that of organizing infarct.

Anatomical Diagnosis: Rheumatic arteritis, coronary artery insufficiency, extreme; rheumatic myocarditis, endocarditis, and pericarditis; pulmonary infarcts, small, multiple, due to pulmonary arteritis.

Case 2. F. C., aged 22 years, of medium height and weight; was examined numerous times in the Navy, including a very carefully recorded examination prior to a herniorrhaphy in 1940. No evidence of heart disease was found. He went through a strenuous tour of duty in the South Pacific during 1943 and early part of 1944. Upon application for an increase in insurance, the consultant at a U. S. Naval Base Hospital reported: "there is a history of rheumatism with swelling of the knees at the age of 14; examination shows a loud systolic and a slight aortic diastolic murmur, heard best at the second right interspace; the blood pressure is 160 mm. Hg systolic and 60 mm. diastolic; patient has an old rheumatic aortic lesion well compensated." "Recommend restriction of extreme strain and over-exertion." He was returned to the continental United States on October 18, 1944, as he complained of shortness of breath while engaged in amphibious training. He was admitted to the sick list on that date. On November 3, 1944, careful physical examination showed slight cardiac enlargement, a systolic murmur at the base of the heart transmitted into the neck vessels but unaccompanied by a systolic thrill, an aortic diastolic murmur heard best in the third left interspace, and a systolic murmur heard best at the apex of the heart and transmitted well into the axilla. The exercise tolerance test showed a resting pulse of 72, after exercise 116 and after one minute rest the pulse was 78. There was no cyanosis and no dyspnea. The temperature and pulse remained normal during 18 days' observation. The electrocardiograms were within normal limits (figure 2). The teleroentgenogram showed 25 per cent enlargement according to the Ungeleider table. The blood count, urinalysis and sedimentation rates were within normal limits. The Kahn test was negative and there were no stigmata of syphilis. He was active on the ward following a program of gradually increased activity. On November 20, at 10:30, he was assigned outside duty, as there were no signs of rheumatic activity

and no signs of limited cardiac or pulmonary reserve. A review of his health record showed no evidence of an active rheumatic process since enlistment within the Navy. It was assumed the heart disease was a well compensated residuum of the rheumatic activity which occurred at the age of 14. The patient went canoeing at noon on November 20, 1944, in company with a qualified life-saver. The patient, who was paddling stern, without any outcry suddenly fell overboard. The patient did not rise to the surface, although he was known to be a strong swimmer and experienced boatman. The body was recovered six hours later.

The *gross pathologic examination* was essentially negative except for the heart and lungs. The lungs floated, and there was crepitation throughout. There was a large amount of fluid in the trachea and bronchi. There was vegetation material in the nares and in the trachea. The pericardium was not thickened and contained 30 c.c. of straw-colored fluid. The heart weighed 500 gm. The right ventricle was dilated; the left ventricle was contracted. The right ventricular wall measured 6 mm., the left 16 mm. The tricuspid orifice measured 10 cm. in circumference; the mitral orifice 8 cm. The tricuspid leaflets were fused and retracted. The mitral leaflets were greatly thickened, fused and the free edge was extremely hard. The aortic valve cusps were thickened and curled. The circumference of the aortic orifice was 7.0 cm. The left coronary artery showed a sclerotic patch near its origin and at 5 cm. from its ostium was greatly narrowed. There was a discolored softened area measuring 30 by 20 mm. in the anterior wall of the heart. The anterior descending branch of the left coronary, leading into this area, appeared occluded by edema of the arterial wall. There were a number of sclerotic patches in the aorta at its origin and elsewhere.

Microscopic pathology: The softened area just described contained an excessive amount of blood, apparently largely intravascular, and a rather curious scattering of eosinophiles. Elsewhere in the myocardium were occasional collections of fibrocytic cells and Anitschow myocytes. The valves showed a remarkable chronic active process, characterized by calcification in some areas, and by vascularization and infiltration by round and large mononuclear cells in others. The aorta showed striking cellular accumulation. There was considerable focal edema in the coronary arteries and endocardium, with fibrosis around coronary arteries. How far the acute edema in these arteries was attributable to submersion could not be determined.

Anatomical diagnosis: Chronic rheumatic endocarditis involving the aortic, mitral and tricuspid leaflets; acute rheumatic arteritis with occlusion of the anterior descending branch of the left coronary artery, and submersion.

Case 3. J. J., aged 26, of asthenic build, was admitted to the sick list on July 25, 1944, complaining of precordial pain and palpitation of six months' duration. The examination showed no cardiac enlargement, a systolic cardiac murmur audible over the entire precordial area, an inverted T_4 wave in the electrocardiogram, and an elevated blood sedimentation rate of 27 mm. per hour (Cutler). On October 4, 1944, the diagnosis of primary atypical pneumonia was made, owing to migrating areas of consolidation in the lungs. On October 13, 1944, the diagnosis of rheumatic fever was made because of the slight fever, persistent tachycardia, systolic cardiac murmur, mildly painful joints, evidence in the lungs of a rheumatic pneumonitis, and the elevated blood sedimentation rate. On June 2, 1945, the patient complained of increased precordial pain. The patient was placed on complete bed rest because of the persistent precordial pain, constantly changing pattern of the T waves in the electrocardiograms and the elevated blood sedimentation rates. With dramatic suddenness the precordial pain increased and death occurred abruptly 8 hours later (figures 3, 4, 5 and 6).

The gross pathologic examination showed marked cyanosis of the lips and nailbeds. The pericardium was not thickened and contained 20 c.c. of straw-colored fluid. The heart weighed 400 gm. The thickness of the right ventricle was 5 mm., the left

14 mm. The circumference of the tricuspid orifice was 11 cm. The tricuspid leaflets were thickened, but moved freely. The circumference of the mitral orifice was 8.5 cm. The mitral leaflets were thickened, but remained competent. The circumference of the aortic orifice was 6 cm., and the leaflets were greatly thickened. The base of the aorta in the region of the sinuses of Valsalva was greatly thickened and distorted. The left coronary artery was extremely narrowed by an atheromatous plaque a short distance from its origin. The descending branch of the left coronary artery appeared to be obliterated by a soft mass. The wall of the left ventricle showed areas of fibrosis suggesting old myocardial infarcts. The lungs were crepitant throughout. There was some congestion in the basal lobes. There were no areas of gross pulmonary infarction. The trachea and pulmonary arteries were patulous. There was a

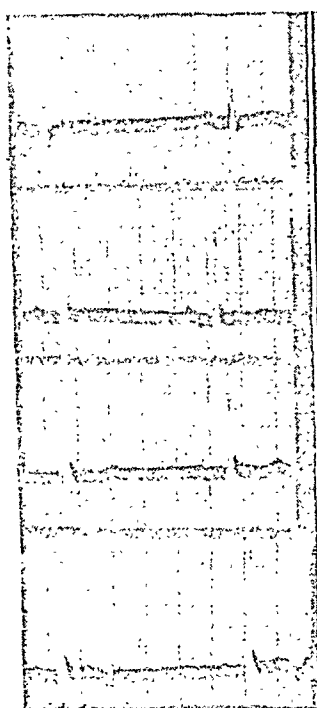


FIG. 4.

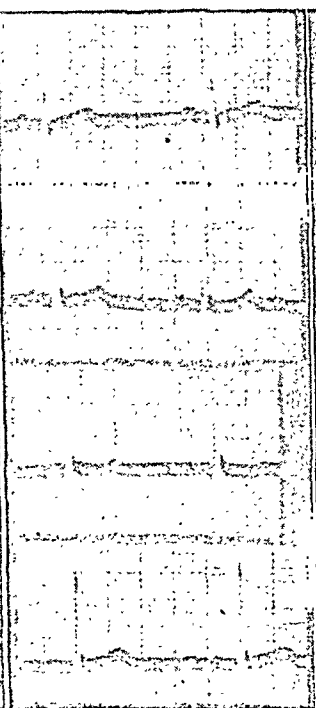


FIG. 5.

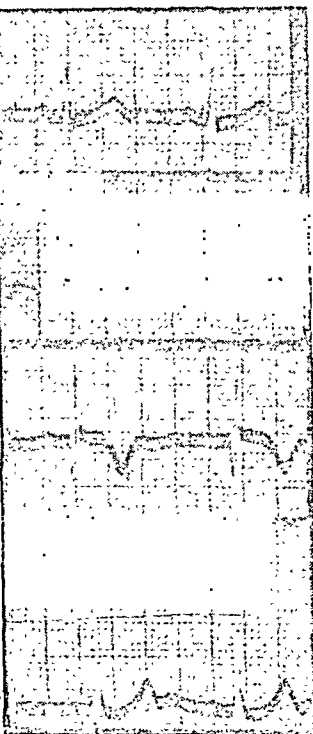


FIG. 6.

soft atheromatous mass in the left internal carotid artery at the point where it enters the Circle of Willis.

In the microscopic study the myocardium was thickly strewn with cellular aggregations which could hardly be called anything but Aschoff bodies. These were for the most part of the "polarized" variety. Many were distorted by fresh hemorrhage. Infarcts of various ages were conspicuous. Large and small coronary arteries showed changes which resembled those found in case 1, save that those in the large arteries were much more cellular. The mitral valve showed fibrinoid material, cellular vegetations, and accumulations of cells deep within the valve. There was conspicuous cellular infiltration and edema in the aortic valve and the base of the aorta, with a large amount of acidophilic "fibrinoid" material in adjacent tissue. The epicardium showed some fibrocytic reaction. In the lungs was periarterial and endoarterial fibrosis, with a few cellular endoarterial vegetations. There was marked proliferation of alveolar endothelium. The liver showed periportal accumulations of mononuclear cells. The material in the internal carotid artery was hyaline and acellular. Hyalinization was

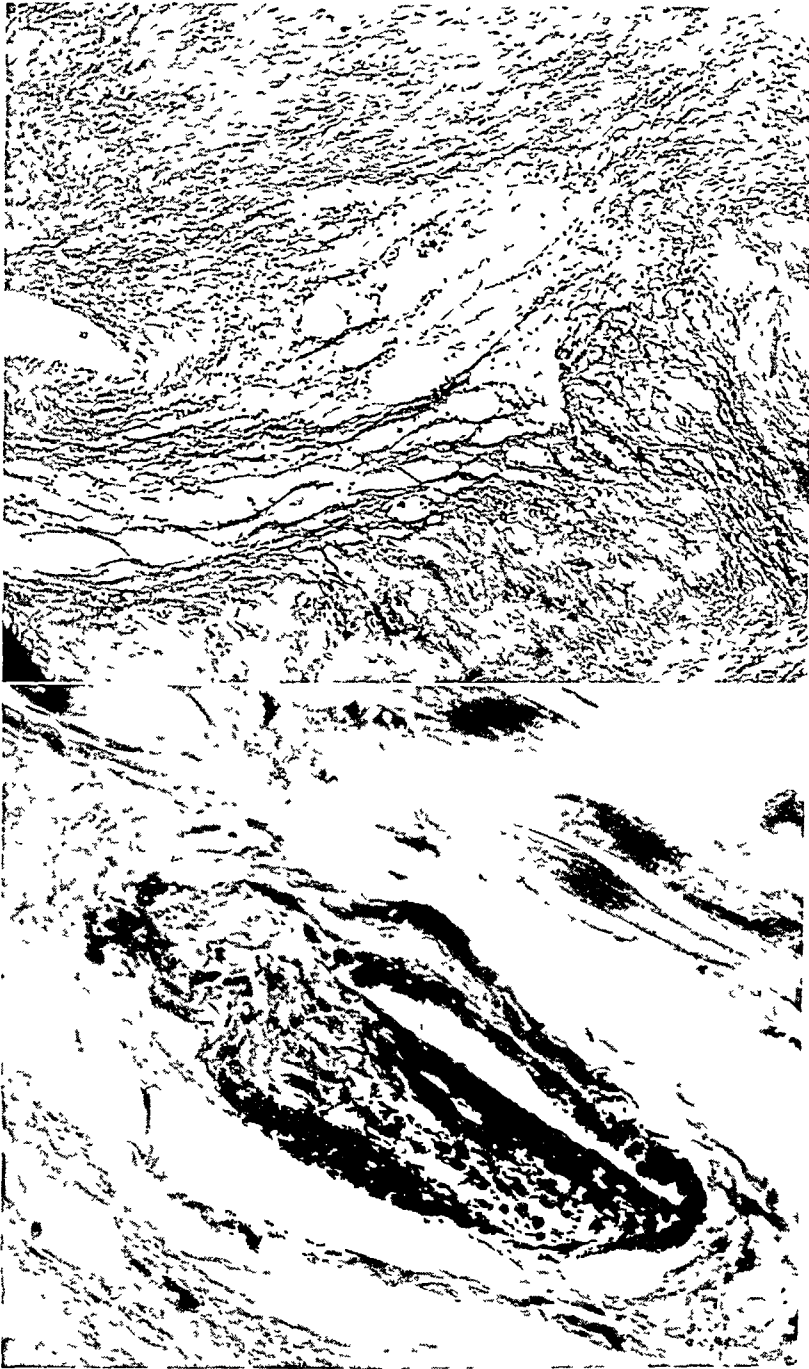


FIG. 7. (above) "Collagenous" mass in wall of coronary artery. Masson Trichrome stain, $\times 70$.

FIG. 8. (below) Cellular reaction in and around small myocardial artery. Masson Trichrome stain, $\times 420$

conspicuous in the glomeruli and in smaller cerebral arteries. In the arachnoid were periarterial cell groups resembling Aschoff bodies.

Anatomical Diagnosis: Acute and subacute rheumatic arteritis and pancarditis; myocardial infarction (figures 7 to 13).

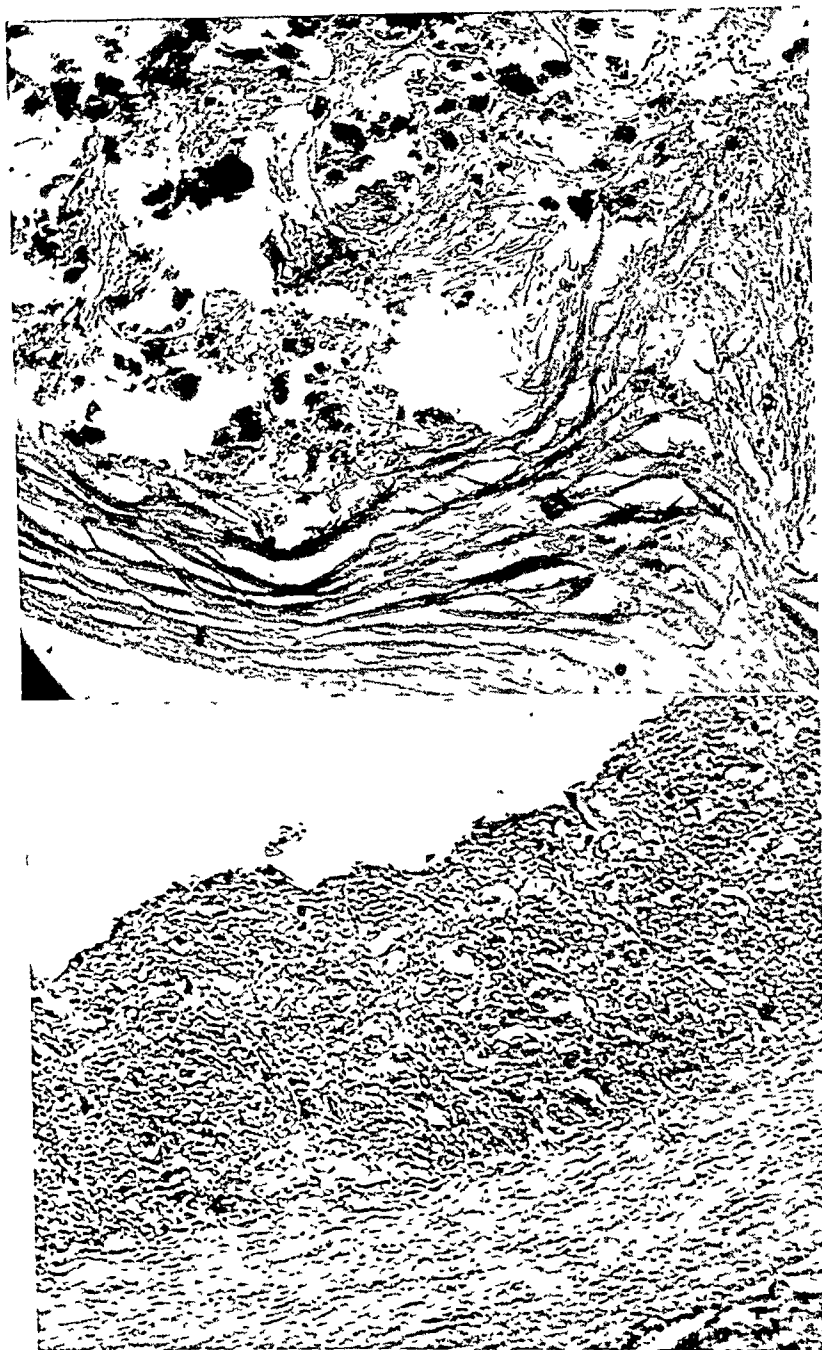


FIG. 9. (*above*) Calcification at base of aortic valve. Van Giesson stain, $\times 70$.

FIG. 10. (*below*) Coronary artery showing mural edema. Van Giesson stain, $\times 125$.

DISCUSSION

Perhaps the most striking common feature in these three cases is the occurrence of distinctive lesions at the base of the aorta. In cases 1 and 3 there was unequivocal histologic evidence of widespread vascular disease,



FIG. 11. (above) Infarcted area showing necrosis of heart muscle and edema and cellular infiltration of endocardium. Van Giesson stain, $\times 90$.

FIG. 12. (center) Coronary artery showing extreme fibrosis, cellular accumulation and vascularization. Van Giesson stain, $\times 90$.

FIG. 13. (below) Higher magnification of area in figure 12 marked by arrow.

particularly in the coronary and pulmonic circuits. The age of these changes cannot be determined by histologic examination. That much of the alteration in the coronary arteries was relatively acute is suggested by the clinical and electrocardiographic histories. In case 3 it seemed probable that the pulmonary vascular changes were related to the episode of "atypical pneumonia." If analogies suggested by recent pathologic and experimental observations are justified, then accumulation of relatively homogeneous acellular material ("hyaline," "swollen collagen" or "fibrinoid") might be considered as a very early histologic manifestation of acute vascular damage. Such a guess would suggest that the coronary disease was more recent in case 1 than in case 3. This suggestion seems corroborated by the absence of histologic evidence of infarction in case 1, and by the clinical and cardiographic records. If the extreme narrowing of coronary lumina in case 1 is as recent as the data suggest, one would, of course, assume that tissue particularly liable to acute swelling had been laid down some time in advance. The pulmonary artery changes in this case seem older than those in the coronaries. The history in case 2 strongly suggests a "stroke" referable to the coronary arteries, and the histologic findings are quite compatible with this notion. However, though the arterial edema is focal, and like that seen in other cases, it is possible that these changes are in part artefact due to submersion. Satisfactory interpretation is therefore difficult.

The question of the justifiability of the rheumatic diagnosis in these cases has been discussed at length elsewhere. It is difficult to see how the valvular changes in case 2 and the myocardial cell groups in case 3 could be called anything else, and in general we think the assumption that arterial and endocardial changes have nothing in common is probably an unreasonable one. The question of whether arterial changes in such cases should be termed rheumatic seems largely a matter of definition, in which the reader is entitled to his own view.

On histologic grounds one could not distinguish between these arteries and those which in the aged would readily be termed sclerotic. It would be imprudent to maintain that the mechanism of acute coronary death in these young individuals with a clinical diagnosis of rheumatic fever or rheumatic heart disease was essentially different from that in older individuals without such a diagnosis. Many of the obvious clinical phenomena in myocardial infarction seem to suggest an acute change rather than an insidiously progressive one, and there seems no reason why the aged should not suffer from acute coronary arteritis. However, in these cases the youth of the patients and the clinical data strongly suggest that the vascular changes are actually acute.

SUMMARY

1. From a total of 13 deaths attributable to rheumatic fever which occurred in a series of rheumatic fever patients observed for a period of 18 months, three deaths were sudden, unexpected and dramatic.

2. In one case rheumatic cardio-angiitis was diagnosed clinically.

3. Gross and histologic studies of the pathological material showed unquestionable evidence of rheumatic fever.

4. The cause of abrupt death in each of the three cases appears to be an acute anaphylactic coronary angiitis superimposed upon a low-grade rheumatic carditis.

Photomicrographs by Mr. Edward N. Hamilton, College of Medical Evangelists, Los Angeles.

BIBLIOGRAPHY

1. HAMILTON, R. L., and ROBERTSON, H.: Electrocardiographic studies of dying heart in angina pectoris, *Canad. Med. Assoc. Jr.*, 1933, xxx, 122-124.
2. MUNCK, W.: Sudden death from heart failure in adults, *Ugesk. f. laeger*, 1931, xciii, 787-794.
3. HILL, I. G. W.: Stimulation of vagus nerve and carotid sinus in man, *Quart. Jr. Exper. Physiol.*, 1932, xxii, 79-93.

THE MALARIA TRIAD¹

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PERIODIC chills with fever,^{1, 2, 3} splenomegaly,^{4, 5} and anemia⁶ have been traditionally recognized and taught^{7, 8, 9} as the diagnostic triad of malaria. Even the most recent publications continue to propagate this dictum.¹⁰ Boyd,¹¹ in 1944, states categorically: "Clinically active malaria infections, regardless of the species of their causative parasite, exhibit three basic symptoms: (a) fever, (b) anemia, (c) splenomegaly."

Recent experience with acute malaria cases, however, leads one to believe that the value of the triad in diagnosis of this disease deserves much reconsideration. True, a patient with typical periodic fever, splenomegaly, and anemia is more than likely harboring plasmodium parasites. But, for a clinician's diagnosis to depend on the appearance of these signs is like waiting for acidosis or coma to diagnose diabetes.

A series of 143 acute malaria cases, proved by blood films, was admitted to a Naval Hospital in Panama between November 15, 1943 and September 1, 1945. The occurrence of the malaria triad in these cases is summarized in chart 1. The group is considered representative in that it includes in-

CHART I

Symptoms	Patients	%
1. Periodic chills and fever (typical) (a) .	9	63.4
Patients with chills and fever (atypical)	81	
Patients with chills .	2	
Patients with "chilliness" .	11	
Patients with fever	47	
Patients with fever (typical) .	5	
2. Palpable spleen	47	33.0
3. Anemia (b)	23	24.7
Erythrocyte count below 3,500,000	3	
Erythrocyte count below 3,000,000	2	
Hemoglobin below 14 grams. .	15	
Hemoglobin below 13 grams. .	8	
(a) The terms typical and atypical refer to tertian or quartan cycles. It is well known that falciparum fevers are frequently not cyclic.		
(b) Complete blood studies are recorded in only 93 cases and the percentage figure is on that basis.		

fections by all three types of plasmodia as follows: *Plasmodium vivax*: 96; *Plasmodium falciparum*: 42; *Plasmodium malariae*: 3; Mixed *Falciparum* and *Vivax*: 1; *Unclassified*: 1. Of these 143 patients, 103 were suffering with their first attack of malaria, whereas in 40 the infection was recurrent.

The small number of cases with anemia is even more significant when it is appreciated that erythrocyte counts and hemoglobin values are generally reduced in the tropics. In 1000 consecutive male admissions to this hospital

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for all reasons the average erythrocyte count was 4,438,000 and the hemoglobin value, 13.7 gm. As Manson-Bahr¹² says: "Pale faces become still paler in the tropics and the condition is likely to progress there."

Numerically, this series is not large. However, our findings in this study closely correlate with observations of others on greater numbers of cases in various parts of the world. This is summarized in chart 2.

Further condemnation of the triad as a means of early diagnosis of malaria is expressed by Talbot,²⁰ and Most and Meleney.²¹ Talbot states:

CHART II

Author	Noehren	Geneway ¹³	MacDonald ¹³	Simpson et al. ¹⁴	Kean and Smith ¹⁵	Gordon et al. ¹⁶	Applebaum and Strager ¹⁷	Hughes and Bomford ¹⁸	Clark ¹⁹	Clark ¹⁹
Location	Panama	China	India and West Africa	South Pacific	Panama	South Pacific	Panama		West Indies	West Indies
No. of patients	143			1184	100	435	125	854	2585	462
Characteristic chills and fever	6.34%				49%	80%				
Characteristic fever	3.5%							57.2%		
Palpable spleen	33%	24%	50%	17.3%	30%	23%	11.2%	36.8%	4.2%	38%
Anemia:										
Less than 3.5 million RBC	3%			7.5%		2.4%				
Less than 3.0 million RBC	2%			4.9%						
Less than 14 grams Hgb	16.1%					26%				
Less than 13 grams Hgb	8.6%					3%				

"We especially had to give up the idea that chills and periodic fevers were constant symptoms of malaria. . . . Cases go undiagnosed because they are never characterized by chills or fever or any textbook course of malaria." Most and Meleney, in discussing *P. falciparum* infections warn that waiting for the triad is dangerous because it does not always exist. They cite a tragic example of such a delay.

Kean and Smith¹⁵ in analyzing 100 deaths from *P. falciparum* infection state: "No particular conclusions could be drawn from a study of the temperature charts. Some patients had high fever, others had little elevation of temperature." Fitz-Hugh et al.²² also found that a few of their cases were "practically afebrile."

Lack of anemia, even in cases with numerous recurrences was noted by Metcalf and Ungar²⁸: "Total counts in 102 patients gave an average of 4.1 million per cu. mm. Only 3 cases dropped below 3 million. Hemoglobin determinations in 44 instances paralleled the erythrocyte level closely, with an average color index of 0.93. Morphologically the red blood cells showed no significant departure from normal. In general, the size, shape, and color of the erythrocytes in these cases did not show remarkable variations."

Absence of splenomegaly has been also observed for some time. Dead-erick²⁴ in 1909, commented: "The value of the enlargement of the spleen in the diagnosis of malaria has certainly been overrated." In the same year Craig²⁵ also stated: "While there can be no doubt that the organ is enlarged the enlargement in many cases is not demonstrable and a very large proportion of cases do not present a palpable spleen."

Further lack of splenomegaly was noted by Kern and Norris,²⁶ in studying liver enlargement in 1153 veterans returning from the Pacific with malaria. They observed: "Enlargement of the liver, like that of the spleen, seemed to follow the course of the disease. It was not palpable at the onset of the disease but enlarged during the first days of the fever." A careful study of the course of splenic enlargement was made by Stratman-Thomas.²⁷ He found, "the degree of splenic enlargement attained is directly proportional to the duration of the clinical attack. Attacks of ten days' duration or less tend to promote palpability only on deep inspiration with the maximum enlargement noted at the end of the second week. This enlargement disappears during the third week after the clinical attack." Hunt,²⁸ after extensive experience with the disease in North Africa feels: "To wait for a positive smear or a palpable spleen costs more lives than to treat a suspected patient." Barber and Rice²⁹ found splenic enlargement "a useful but not very accurate measure of the amount and distribution of malaria in Egypt."

Strong¹³ summarizes the situation as follows: "While there has been considerable difference of opinion from time to time about splenic index in the diagnosis of malaria, palpability of the spleen, temperature curves and cyclic manifestations should not generally be considered by the practitioner reliable for the diagnosis without microscopical examination." We fully agree with Strong's statement and might add that it is dangerous to wait for these signs before doing a microscopical examination of the blood.³⁰

An explanation of this change in significance of the malaria triad is not difficult to find. One of the fundamentals underlying the progress of medicine in recent decades has been earlier recognition and diagnosis of disease. No longer must a mass be palpable in the abdomen to suggest cancer of the stomach. Neither must a patient be jaundiced to diagnose liver disease.

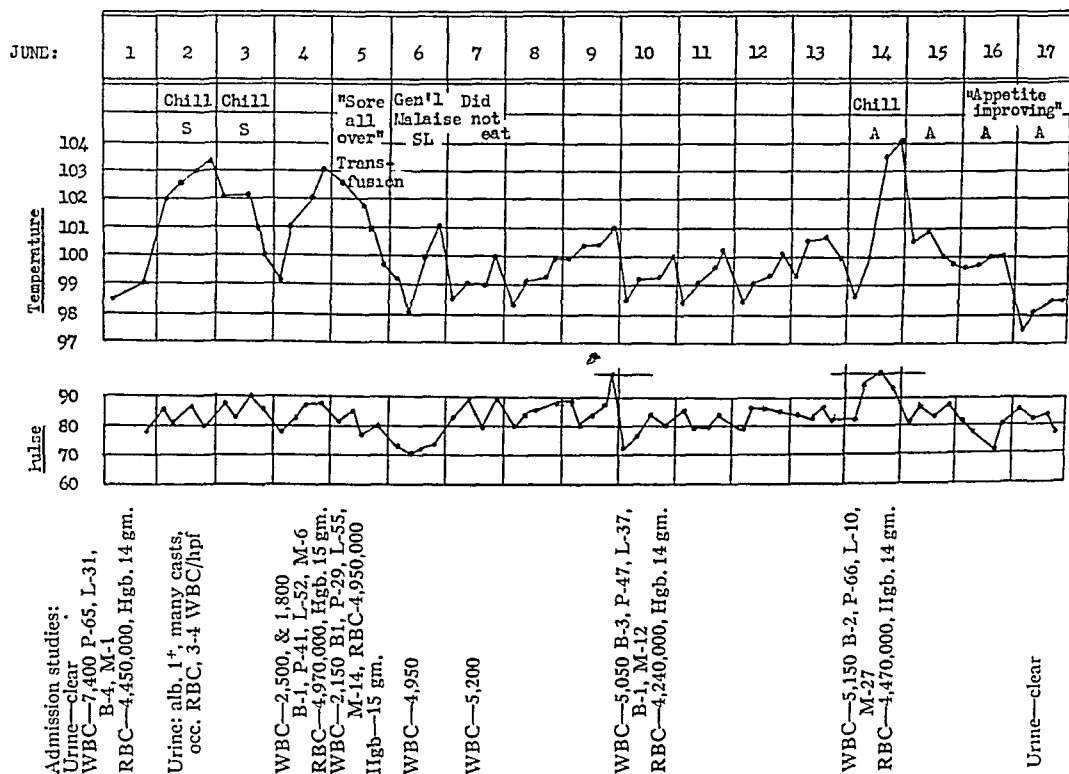
The same is becoming true of malaria. Patients, especially military personnel, are accessible to medical observation before the signs of established infection have developed. In our group of malaria cases (except for eight patients whose history exceeded 21 days), the average duration of complaints before admission was only 4.4 days. Many were seen in the first hours of

discomfort. The complaints, then, as we saw them, were really what textbooks have long called the "prodromal signs"^{31, 32} of malaria. The triad of periodic chills with fever, anemia, and splenomegaly, is a later manifestation of an established plasmodium infection. Its clinical value must be reconsidered in that light, for the diagnosis of acute malaria is now made before that triad develops.

The temporal relationship of malaria symptoms and signs was fairly well demonstrated by patients in this group who developed clinical malaria while hospitalized for unrelated conditions:

A 34 yr. white F2/c was admitted to the surgical service on May 4, 1944, with the diagnosis: "Dislocation, right shoulder." No temperature or systemic complaints were noted for the first 16 days, after which a Nicola operation was performed on his shoulder. For seven days post-operatively he had an afternoon elevation of temperature never exceeding 100° F. The next five days were completely afebrile. On his thirtieth hospital day he had a chill rather suddenly and a fever of 103.4° F. His clinical course from that time on is charted below (chart 3). Blood films for malaria

CHART III



(S—sulfadiazine therapy (total—7 gm.), SL—serious list; A—atabrine therapy)

were examined repeatedly for three days, June 3 to 6. All were negative for malaria parasites. The spleen was never palpable. June 14 he had another chill and rise of temperature to 104° F. At that time *Plasmodium vivax* was found. A routine course of atabrine (total 2.6 gm.) resulted in an uneventful recovery. He was discharged asymptomatic on July 31, 1944. No history of previous malaria infection was obtained on questioning the patient.

A similar episode occurred in a 19 yr. white SM 3/c from whom a suppurative appendix was removed on July 4, 1944. He ran a low-grade postoperative fever for 10 days, after which he was afebrile for eight days. The following day he noted "malaise, headache," and a temperature of 102° F. This continued for five days, with urinary and blood findings almost identical to those of the other case. At this time he was starting to show the tertian fever cycle, and his blood was found to contain *Plasmodium vivax*. Atabrine in the usual dosage produced an uneventful recovery. There was no history of previous malaria infection. Following three days of sulfadiazine therapy this patient also showed agranulocytosis (white blood cells 3000, with 4 band, 9 segmented, 71 lymphocytes, 1 eosinophile, and 15 monocytes). The sulfadiazine may³³ or may not^{34, 35} have affected somewhat the course of the infection, but the sequence of symptoms and signs was fairly typical. It is a reasonable assumption, on the basis of other acute cases seen here, that the triad may have become apparent later in each case if atabrine had not been started.

Failure to recognize the "prodromal" complaints as of malarial origin has caused numerous diagnostic errors, some of which have been tragic and fatal.³⁶ Kean and Smith¹⁵ found that in 100 fatal cases of estivo-autumnal malaria, 23 had symptoms of not more than one day before hospitalization, and yet they died. Even in Panama, where, in the minds of many, malaria is practically synonymous with the region, less than 72 per cent of our malaria patients were hospitalized with suspicion of the correct diagnosis, and only 28.5 per cent admitted with the correct diagnosis established.³⁷

These errors would be less significant if it were not true that the early complaints in malaria cases possess rather consistent similarities. The pattern, as seen in our group, was characteristic enough so that even the ward corpsmen could make a fairly accurate diagnosis before the blood film report was available.

Six complaints have been found most helpful: fever, headache, malaise, backache, anorexia, and "foul smelling" perspiration. The diagnosis of malaria was established in a significant number of patients who manifested any four of these six complaints.

✓ *Fever* has always been suggestive of malaria, especially when associated with chills. It is not always present, however, much less so in its typical cyclic form, as has already been mentioned. Fever was noted in 96.7 per cent of our group; in 63.4 per cent associated with chills. No appreciable fever was present in 12 patients on admission.

✓ *Headache* was a symptom in 73 per cent of our patients with malaria. From more careful questioning of recent cases it is apparent that this percentage would be higher if the various admitting examiners had asked specifically for this complaint. The headache is characteristically, though not always, frontal or retrobulbar, with common reference to it as a "tired" or "strained" feeling in the eyes.

✓ *Malaise* is a common complaint in many diseases. It assumes an identifying place in malaria for its sudden and unexplainable onset. It frequently is the first sign in a man who is perfectly all right until this sudden "ache

all over," "tired," or "dragged out" feeling seizes him. This was seen in 71 per cent of our cases, and in 40 per cent was mentioned as the chief complaint.

Backache was complained of by 32.4 per cent of our patients. In all probability it was included even more often under the symptom of malaise. It is characteristically in the lumbo-sacral area, and occasionally severe enough to require morphine.

Anorexia was a prominent complaint in 44 per cent of our cases; associated with vomiting in 9.2 per cent. As additional diagnostic evidence it is valuable. Rarely has a good appetite been seen in a man acutely ill from malaria. In the course of treatment the disappearance of anorexia is a valuable indication of the clearing of these parasites from the blood. Persistence of anorexia is highly suggestive that the treatment has been inadequate and further study of blood smears, especially for gametocytes, should be made.

Foul perspiration has a peculiar sour odor described by patients as like the smell of "burned matches," "phosphorus or sulfur." This symptom was first pointed out by a native of Panama who had experienced malaria paroxysms several times. It has since proved of some diagnostic value. Although noted in only 26.6 per cent of our cases, it was identified by them as something unusual. When present it was quite an accurate indication of a positive blood film.

Other observers have noted the above complaints with similar frequency. Gordon et al.¹⁶ found them in the following percentage in their group of 435 soldiers evacuated from the Southwest Pacific: Malaise, weakness, 97 per cent; headache, 96 per cent; generalized aches, 88 per cent; backache, 88 per cent; nausea, 59 per cent; vomiting, 36 per cent. Hughes¹⁸ reports that in 1200 cases in West Africa, "the main symptoms of the attack irrespective of type and in order of frequency were: headache, backache, shivering, vomiting, feverishness, pain in the back of the neck, generalized aching, slight cough, sweating, and simple diarrhea."

Craig²⁵ in 1909 wrote: "In all cases of malaria there is loss of appetite, often observable for days before the onset of the febrile paroxysm. . . . Headache occurs in practically every case. . . . Pain in back and limbs is always present during acute attacks of malaria and may be very severe." Bercovitz³¹ says: "In most instances, for a few days before the occurrence of the actual malarial paroxysm the patient complains of aching bones and joints, pain in the back and legs, more or less malaise, anorexia, headache, etc."

Polumorovinov³⁸ and Troitzky,³⁹ reporting the deaths of 34 children in Russia, observed: "The children who succumbed showed no constitutional anomalies, the main subjective symptom being severe headache." Fitz-Hugh et al.²² studied 189 cerebral malaria cases and found that: "In all in whom an adequate history was obtainable, headache was severe. Photophobia and vertigo were frequent complaints."

Although these symptoms have occurred with significant frequency, they are not proposed as being diagnostic for malaria but only as highly suggestive of the disease. A great deal has been written lately of the bizarre symptoms of malaria. In fact, malaria has quite indisputably joined syphilis as another great medical "mimic,"⁴⁰ simulating as it does, almost every known disease of the body.

A few of the other findings frequently mentioned in malaria are: upper respiratory changes,⁴¹ hepatomegaly, elevated sedimentation rates, leukopenia, urinary changes, false positive serologic reactions,⁴² bradycardia,¹⁸ jaundice, herpes, and cerebral manifestations.⁴³

In our cases 23.6 per cent had upper respiratory complaints or findings. In fact 13.6 per cent were admitted with a diagnosis of an upper respiratory or catarrhal fever. Hepatomegaly was noted in 11.9 per cent. Of the sedimentation rates examined on admission (24) only 30 per cent were elevated, which is contrary to the experience of Wood⁴⁴ who found 84 per cent elevations. Leukopenia (under 5000) was present in 19 per cent on admission, and leukocytosis (over 10000) in 4.2 per cent. Urinary changes consisting of varying degrees of albuminuria, casts, erythrocytes and leukocytes were seen in 19.7 per cent of the cases. These changes cleared with the treatment of the malaria.

Of the Kahn tests made on all the malaria patients the day after admission, only 5, or 3.3 per cent were positive. This is essentially in agreement with what Bates⁴⁵ has found on admission serologic tests. The fact that the blood was drawn on admission rather than in the later days of the disease may explain the variance with reported figures of 9.9 to 80 per cent,⁴⁶ 100 per cent,⁴⁷ 47.5 per cent,⁴⁸ and 12.5 per cent⁴² false positive reactions.

Bradycardia was frequently a helpful sign. In a new patient with a high fever, the presence of a pulse rate considerably less than the expected 10 points acceleration for each degree of temperature elevation (as seen in fevers of bacterial infection) strongly suggested malaria. Jaundice was present in one case. Herpetic sores were seen occasionally. Cerebral manifestations were seen in one man who was admitted with ataxia and difficulty in speaking.

This series of malaria patients has been reviewed in an attempt to show some consistency in symptoms in spite of the protean nature of the disease. To depend, however, entirely on these "consistencies" would be as fallacious as waiting for the ague-splenomegaly-anemia triad, but like the triad, they should be strongly suggestive. The diagnosis then rests on a blood film examination.

The failure to consider malaria and to do a usually simple blood film examination has been the source of most serious difficulties. Craig⁴⁹ feels, "If there is one fact that experience has proved in the realm of diagnosis, it is that without a blood examination one can never be sure of the diagnosis of malaria and hundreds, and the writer believes, thousands of lives have been sacrificed because of the neglect of this procedure by the practicing physi-

cian." It might also be emphasized here that a single negative smear does not rule out malaria. Frequently several thick and thin films, taken at various intervals, must be examined carefully before final diagnosis is made.⁵⁰

The significance in all this may not be apparent to the practicing physician in civilian life, especially those in temperate climates, although they are aware that malaria has become *the* disease of World War II. They also realize that a few of the thousands of recurrent malaria cases among military personnel⁵⁰ may be in their hands in the next years. But all do not appreciate that *new* cases are also imminent.

The recurrent cases are often the easiest to diagnose. The patient himself recognizes the "feel" of malaria, an invaluable and reliable assistance in diagnosis. It must, however, be differentiated from the recently described "psychogenic malaria."⁵¹

With these recurrent cases at home, new infections are very likely to appear. Conditions in most of the United States, even in the most temperate areas, are as suitable today for the propagation of malaria as they were a century and less ago when the disease was common. There is ample evidence of the malariousness of the country in the pioneer period of the late eighteenth and nineteenth centuries. Not only the old malarious colonies of the East Coast, but all the new states with a more northern location, Indiana, Michigan, western New York, Kansas, Oklahoma, Missouri, Minnesota, Wisconsin, Illinois, and Iowa, all shook with the "ague."⁵²

In New York City during the six years ending in 1890, the statistics show 2,060 deaths or 24.62 per 100,000 from malaria. In Baltimore there were 834 deaths or 41.51 per 100,000, and in Brooklyn 1,413 deaths or 32.62 per 100,000. Although the accuracy of these figures has been justifiably doubted by Thayer,⁵³ it is known that in the first half of the nineteenth century New York and Philadelphia and their environs were intensely malarious.

Packard⁵⁴ records the wide prevalence in places as far north as Madison Barracks, N. Y., Fort Winnebago, Wisc., and Fort Mackinaw, Michigan, and throughout the length and breadth of the Mississippi.

Christian⁵⁵ speaks of malaria in New England where it prevailed "extensively." It has been said that families in the Connecticut Valley had quinine on the dinner table, to be sprinkled on food like sugar, to prevent the "ague." Longfellow, referring to malaria, spoke a familiar warning in *Evangeline*:⁵⁶

Only beware of the fever, my friends, beware of the fever!
For it is not like that of your old Arcadian climate,
Cured by wearing a spider around one's neck in a nutshell.

Ackerknecht⁵² says malaria was so prevalent that it was *the* American disease during the nineteenth century. He cites one of the most striking experiences, that of a French traveler, Comte de Volney. On a 700 mile trip from Cincinnati to Detroit in September 1796, he did not find 20 homes which were free of malaria.

It is felt ⁵⁷ that there is little imminent danger of any serious epidemic of malaria in the United States at present. However, the conditions for transmitting the disease are still present, as is illustrated by a small epidemic which occurred in 1928 in Flint, Michigan. It was the result of southern workers who were carriers of the infection coming to work in automobile factories. In recent years there have also been outbreaks in southern Minnesota, eastern Iowa, northern Ohio, and in Camden, N. J. In the summer of 1943 an outbreak of 53 cases occurred in a small town in Illinois.⁵⁸

Malaria has thus become an important subject for all medical men, military and otherwise. The triad of periodic chills with fever, anemia, and splenomegaly as a diagnostic criterion, should be seriously reconsidered by everyone concerned.

SUMMARY

1. Periodic chills with fever, anemia, and splenomegaly have been traditionally recognized and taught as the triad of malaria. Recent experience with acute cases indicates this triad no longer constitutes the key to diagnosis.

2. So-called "prodromal" complaints are sufficiently consistent to suggest the diagnosis at earlier stages of the disease. These include fever, headache, malaise, backache, and "foul-smelling" perspiration.

3. The final diagnosis still rests on finding the parasite in a blood film. Failure to consider the disease and this usually simple means of diagnosis has resulted in many errors, some fatal.

4. Conditions for ready propagation of the disease from returning military personnel prevail in most parts of the United States, even in the northern states where malaria was once endemic. The situation promises to affect many clinicians to whom malaria is an unfamiliar disease, remembered primarily for its triad of periodic chills with fever, anemia, and splenomegaly.

BIBLIOGRAPHY

1. CELSUS, A. C.: Of medicine in eight books, Trans., with notes critical and explanatory by James Grieve, London, 1756, pp. 114.
2. HIPPOCRATES: Epidemics, Book I, The genius works of Hippocrates, trans. by Francis Adams, London, Sydenham Society, 1859, pp. 368.
3. MAJOR, R. H.: Classic descriptions of disease, 1939, C. C. Thomas, Baltimore, pp. 63.
4. The Merck Manual, 1940, Merck & Co., Rahway, N. J., pp. 704.
5. YATER, W. M.: Fundamentals of internal medicine, Ed. 2, 1944, Appleton-Century, New York, pp. 766.
6. COGGESHALL, L. T.: War malaria, Med. Clin. North Am., 1943, xxvii, 623.
7. Malaria, in the Encyclopedia Britannica, 1943, Encycl. Britt. Ltd., Chicago, Vol. xiv, pp. 726.
8. Handbook of the Hospital Corps in the U. S. Navy, 1939, U. S. Government Printing Office, Washington, pp. 706.
9. YATER, A. B.: Symptom diagnosis, Fourth Ed., 1942, Appleton-Century, New York, pp. 529.
10. ACKERKNECHT, E. H.: The development of our knowledge of malaria, Ciba Symposium, 1945, vii, 38.

11. BOYD, M. F.: Present day problems of malaria infections, Jr. Am. Med. Assoc., 1944, cxxiv, 1180.
12. MANSON-BAHR, P. H.: Manson's tropical diseases, Ed. 11, 1943, Williams and Wilkins, Baltimore, pp. 7.
13. STRONG, R. P.: Stitt's Diagnosis, prevention, and treatment of tropical diseases, Ed. 6, vol. 1, 1942, Blakiston, Philadelphia, pp. 81.
14. SIMPSON, LEAKE, McMAHON, GUDEX, and RUECKERT: Experiences with malaria at an advanced base in the South Pacific, U. S. Nav. Med. Bull., 1943, xli, 1588.
15. KEAN, B. H., and SMITH, J. A.: Death due to estivo-autumnal malaria, Am. Jr. Trop. Med., 1944, xxiv, 317.
16. GORDON, H. H., MARBLE, A., LIPPINCOTT, S. W., BALL, A. L., ELLERBROOK, L. D., and GLASS, W. W.: Clinical features of relapsing *Plasmodium vivax* malaria in soldiers evacuated from the South Pacific area, Arch. Int. Med., 1945, lxxv, 159.
17. APPLEBAUM, I. L., and SHRAGER, J.: Pneumonitis associated with malaria, Arch. Int. Med., 1944, lxxiv, 155.
18. HUGHES, S. B., and BOMFORD, R. R.: Clinical features and treatment of malaria in British troops in West Africa, Brit. Med. Jr., 1944, i, 69.
19. CLARK, H. C., COMP, W. H. W., and JOBBINS, D. M.: A ninth year's observations in malaria in Panama, Am. Jr. Trop. Med., 1940, xx, 47.
20. TALBOT, D. R.: New aspects of malaria, Jr. Am. Med. Assoc., 1943, cxxiii, 193.
21. MOST, H., and MELENEY, H. E.: Falciparum malaria, Jr. Am. Med. Assoc., 1944, cxxiv, 71.
22. FITZ-HUGH, C. T., PEPPER, D., and HOPKINS, H. V.: The cerebral form of malaria, Bull. U. S. Army Med. Dept. No. 83 (Dec.) 1944, pp. 41.
23. METCALF, R. H., and UNGAR, J.: Relapsing malaria, U. S. Nav. Med. Bull., 1944, xliii, 865.
24. DEADERICK, W. H.: A practical study of malaria, 1909, W. B. Saunders, Philadelphia, pp. 256.
25. CRAIG, C. F.: The malarial fevers, 1909, Wm. Wood, New York, pp. 190.
26. KERN, R. A., and NORRIS, R. F.: Liver involvement in malaria, U. S. Nav. Med. Bull., 1944, xliii, 847.
27. STRATMAN-THOMAS, W. K.: Studies on benign tertian malaria: observations on splenomegaly, Am. Jr. Hyg., 1935, xxi, 362.
28. HUNT, T. C.: Medical experience in North Africa, 1943-44, Brit. Med. Jr., 1944, ii, 495.
29. BARBER, M. A., and RICE, J. B.: Survey of malaria in Egypt, Am. Jr. Trop. Med., 1937, xvii, 436.
30. CRAIG, C. F.: Laboratory diagnosis of protozoan diseases, 1942, Lea and Febiger, Philadelphia, Chapt. xx, pp. 278.
31. BERCOVITZ, Z. T.: Clinical tropical medicine, 1944, Paul B. Hoeber, Inc., New York, pp. 161.
32. CRAIG, C. F.: in Tice, Practice of medicine, vol. 3, 1943, W. F. Prior, Hagerstown, pp. 598.
33. COGGESHALL, L. T.: Selective action of sulfonamides on experimental malaria in monkeys in vivo and in vitro, Jr. Exper. Med., 1940, lxxi, 13.
34. COGGESHALL, L. T., MARTIN, W. B., and BATES, R. D.: Sulfadiazine in the treatment of relapsing malarial infections due to *Plasmodium vivax*, Jr. Am. Med. Assoc., 1945, cxxviii, 7.
35. FAGET, G. H., PALMER, M. R., and SHERWOOD, R. O.: Unsuccessful treatment of malaria with sulfonamide compounds, Pub. Health Rep., U.S.P.H.S., 1938, liii, 1364.
36. HYMAN, A. S.: Clinical masquerades of malaria; observations in South Pacific combat areas, U. S. Nav. Med. Bull., 1945, xlv, 287.
37. NOEHREN, T. H.: Malaria in Panama, U. S. Nav. Med. Bull., 1946, xlvi, 877.
38. POLUMOROVINOV, A. D.: Pernicious form of tertian malaria occurring in Riazan Province, Med. Parasitol. and Parasit. Dis., 1943, xii, 65.

39. TROITZKY, S. A.: Severe tertian malaria in Gorky Province in 1941, *Med. Parasitol. and Parasit. Dis.*, 1943, xii, 71.
40. Memoranda on Medical Diseases in Tropical and Sub-tropical Areas, Ed. 1st Am., 1942, Chemical Publishing Co., Brooklyn, pp. 142.
41. STIRK, E. M.: Pulmonary signs in malaria, *Jr. Roy. Nav. Med. Serv.*, 1943, xxix, 272.
42. DAWBER, T. R.: On the importance of malaria as a cause of false positive serologic reactions, *Ann. Int. Med.*, 1943, xix, 651.
43. MCGINN, S., and CARMODY, J. T. B.: Cerebral symptoms in malaria, *U. S. Nav. Med. Bull.*, 1944, xliii, 1157.
44. WOOD, P.: The erythrocyte sedimentation rate in infective hepatitis and in malaria, *Brit. Med. Jr.*, 1945, i, 9.
45. BATES, L. B.: Board of Health Laboratory, Gorgas Hospital, Ancon, C. Z. (Personal communication).
46. TAUSIG, A. E., and DEGEL, M. N.: Kahn test in malaria, *Jr. Lab. and Clin. Med.*, 1933, xxii, 614.
47. KITCHEN, S. F., WEBB, E. L., and KUPPER, W. H.: The influence of malaria infections on the Wassermann and Kahn reactions, *Jr. Am. Med. Assoc.*, 1939, cxii, 1443.
48. ROSENBERG, A. A.: Effect of malaria on serological tests for syphilis, *Bull. U. S. Army Med. Dept.*, No. 84, pp. 74-80 (Jan.) 1945.
49. CRAIG, C. F.: in Blumer, *Bedside diagnosis by American authors*, 1929, W. B. Saunders, Philadelphia, pp. 346.
50. DIEUDAIDE, F. R.: Clinical malaria in wartime, *War Med.*, 1945, vii, 7.
51. MERRILL, B. R.: Psychogenic malaria, *U. S. Nav. Med. Bull.*, 1945, xlv, 60.
52. ACKERKNECHT, E. H.: Malaria in the United States, *Ciba Symposia*, 1945, vii, 63.
53. THAYER, W. S.: *Lectures on the malarial fevers*, 1901, D. Appleton, New York, pp. 272.
54. PACKARD, F. P.: *History of medicine in the United States*, 1931, Paul Hoeber, New York, pp. 633.
55. CHRISTIAN, A. M.: Osler's, *The principles and practice of medicine*, Ed. 14, 1942, D. Appleton-Century, New York, pp. 443.
56. SCOTT, H. H.: *A history of tropical medicine*, 1942, Williams and Wilkins, Baltimore, vol. I, pp. 218.
57. *Medicine and War*, *Jr. Am. Med. Assoc.*, 1944, cxxvi, 307.
58. MCCOY, O. R.: Imported malaria, *Am. Jr. Pub. Health*, 1944, xxxiv, 15.

THE MEDICAL MAN AND THE CONSTITUTION *

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MEDICAL STANDARDS

LICENSE REQUIRED

IN his opinion in *Lambert v. Yellowley*¹ Mr. Justice Brandeis uttered the following dictum: "Besides, there is no right to practice medicine which is not subordinate to the police power² of the states. . . ."

One decision cited by Mr. Justice Brandeis to support his dictum was *Dent v. West Virginia*.³ That state in 1882 passed a statute which required every medical practitioner to meet one of three standards: (1) a graduate of a reputable medical college; (2) a practitioner in West Virginia continuously for ten years prior to March 8, 1881; or (3) pass an examination prepared by the State Board of Health. Dr. Dent had only practiced since 1876. He had a diploma from the American Medical Eclectic College of Cincinnati, Ohio, but that college had been determined by the Board of Health not to be "reputable." Dr. Dent did not submit himself to the examination of the board. He was convicted for violating the West Virginia statute. The Supreme Court of the United States affirmed the conviction and thus determined that the statute was no violation of due process guaranteed by the Fourteenth Amendment. There are many similar decisions.⁴

LICENSE REVOCABLE

Licenses to practice medicine may be revoked by a state board. The courts generally have refused to hold that statutes conferring this power violate constitutional provisions. The usual claim has been that due process was denied. More particularly it has been argued that statutes permitting revocation were unconstitutional because the grounds for revocation were stated in general terms, such as gross immorality or unprofessional conduct. Most courts have not been convinced by this argument.⁵ Some of them, however, have held that such grounds are so vague as not to give fair notice. Such a defect, according to the minority view, makes a revocation of license statute unconstitutional.⁶

DISCRIMINATION

Statutes regulating members of the several professions practising the healing arts do not have to treat each profession precisely the same. The test, when complaint is made that the statutes deny equal protection of the

* Received for publication April 1, 1946. The following discussion is not closely confined to constitutional problems; nor is it limited to physicians and surgeons.

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laws (class legislation), is whether the discrimination is plainly unreasonable.⁷ Louisiana discriminated against chiropractors by requiring them to pass satisfactory examinations in the same subjects that were specified for physicians and surgeons, including surgery and materia medica. Other statutes provided for the admission of osteopaths, dentists, chiropodists, and trained nurses without requiring them to take a full course in materia medica or surgery. In other words, the osteopaths were favored and the chiropractors were, it would appear, practically prevented from practising in Louisiana. But this patent discrimination was sustained by the Louisiana Supreme Court.⁸ It stated: "Were it otherwise the legislature would be greatly hampered in the exercise of its power to protect the general health and the public from imposition and fraud. Every group of men who might get together and evolve some system, designed to restore health, would be entitled to recognition, and all that could be required of them would be evidence of good character and a knowledge of such subjects as their particular school seemed to require, although the legislature might deem with reason a knowledge of such subjects wholly insufficient to entitle any one to treat the sick." This reasoning by the Louisiana Supreme Court does not appeal to this writer as a perfect example of logic. The states should have the power to deny recognition to schools of medicine that are not valuable to society.⁹ That fundamental proposition would hardly be denied by any disinterested person. But should a state be permitted to require standards for chiropractors in excess of those for osteopaths? However, even if the answer to this question must be in the negative, it would not necessarily follow that Louisiana could not properly deny admission to chiropractors. Conceivably its board might have reasonably determined that the chiropractors failed to present "a diploma from a college in good standing." Perhaps there was at that time no such college teaching the system known as chiropractic.

Probably it is not of much importance now, but in establishing a standard of education as a condition to securing a license, it is no violation of equal protection to make a reasonable exception in favor of established practitioners.¹⁰ The Minnesota legislature in 1919 revised its statutes concerning the practice of dentistry. Section four of this revision authorized the board of dental examiners to suspend or revoke dental licenses for a number of specified reasons. Section eight had a sweeping provision in this language: "provided that the provisions of this act shall not apply to persons lawfully engaged in the business or practices of dentistry at the present time." It is a fair guess that the legislature intended merely to permit dentists licensed before 1919 to continue to practice without qualifying again for a new license. But the Minnesota Supreme Court held that section eight plainly excluded these dentists from the disciplinary provisions of section four. This discrimination was a violation of constitutional provisions for equality and thus made the revision invalid.¹¹

In a Florida case, T. K. Jones stated that he had taken three examina-

tions given by the Florida State Board of Dental Examiners; that he had been thrice notified that he had failed to pass; but that he had made as high a mark as others who were granted certificates to practice by the Board. Accordingly, Jones claimed that he had been refused a certificate capriciously and from prejudice. After the board's motion to quash the proceedings had been overruled, the board declined to give any further answer to Jones' complaint. Thus the actual facts were not adequately developed. But on the meager showing it would appear that the Florida court acted correctly in compelling the board either to justify its conduct or to issue a certificate to him. To do otherwise would seem to violate the constitutional guaranty of equal protection; but this provision was not mentioned by the Florida Supreme Court.¹²

ADVERTISING

Oregon passed a statute that placed severe limitations upon the advertising permitted by dentists. The Supreme Court of the United States held that the statute was valid, saying: (1) "Nor has plaintiff any ground for objection because the particular regulation is limited to dentists and is not extended to other professional classes. The state was not bound to deal alike with all these classes, or to strike at all evils at the same time or in the same way. It could deal with the different professions according to the needs of the public in relation to each;" and (2) that defendant was not justified in advertising in the forbidden manner merely because his advertisement was truthful. The court also observed: "The legislature was not dealing with traders in commodities, but with the vital interest of public health, and with a profession treating bodily ills and demanding different standards of conduct from those which are traditional in the competition of the market place. . . . And the community is concerned in providing safeguards not only against deception, but against practices which would tend to demoralize the profession by forcing its members into an unseemly rivalry which would enlarge the opportunities of the least scrupulous. What is generally called the 'ethics' of the profession is but the consensus of expert opinion as to the necessity of such standards."¹³

CORPORATE PRACTICE

Despite a dissenting minority, it has been generally agreed by the courts that neither a corporation for profit nor any other unlicensed person may practise medicine, surgery, or dentistry through licensed employees. Such a policy by a state does not offend constitutional provisions.¹⁴

Apparently in no state have private corporations for profit made more determined efforts to practice medicine and dentistry than in California. They were denied this right when the effort was directly attempted. Then they made an indirect effort as disclosed by the opinions in *People ex rel. State M. Exrs. v. Pacific Health Corp.*¹⁵ This corporation for a premium

agreed to pay the policy holder for medical services rendered to him; but to obtain this benefit the holder "must, save as to emergency expenses not exceeding \$50, accept a doctor from the list" of physicians and surgeons approved by the corporation. This restrictive provision appears to be the main point of difference between this corporation and other insurance companies which issue the long accepted ordinary health and accident policy. The defendant, Pacific Health Corporation, was operating for profit and was seeking to make as many of its contracts as possible. But the Supreme Court of California held that it was illegally engaged in the practice of medicine in excess of its corporate powers. The court refused to heed the argument made by the corporation that the doctors on its approved list were independent contractors as opposed to employees in other cases where corporations were found to be practising medicine. This was rejected as a technical distinction and the court reasoned thus: "The evils of divided loyalty and impaired confidence would seem to be equally present whether the doctor received benefits from the corporation in the form of salary or fees. And freedom of choice is destroyed, and the elements of solicitation of medical business and lay control of the profession are present whenever the corporation seeks such business from the general public and turns it over to a special group of doctors." To answer objections made by the three judges who dissented, that the decision would be a peril to "fraternal, employee, and hospital associations and various medical-hospital services [that] have been rendering such services to their members through doctors employed by them" and also to health insurance and group medicine, the majority of the court was happy to say: "It is perfectly possible to bring adequate medical service to the vast numbers of people who now can ill afford it by some means which will protect both the profession and the public from the evils of corporate control of the practitioner." Then the majority cited as an example of what it had in mind, *Butterworth v. Boyd* decided the same day. That case is discussed in the next paragraph.

In 1937 the city and county of San Francisco established a health service system for all of its employees who were members of the retirement system, including the teachers and employees of the board of education. The system was to be administered by a board to be elected by the members of the system. Members of religious sects who believed in healing by prayer were exempted from the system at their option. The board had the power to exempt those whose annual salaries exceeded \$4,500, and those who had otherwise provided for adequate medical care. The board had the power to adopt (1) a plan for medical care, (2) for indemnification of the costs of medical care, or (3) for carrying insurance against such costs. To pay the expense of the system the board could determine the monthly sum to be deducted from the compensation of the members. From the fund so obtained all expenses of the system were to be paid. Members in seeking medical care were free to select their physicians, nurses, hospitals, etc., subject to these restrictions only: (1) the rules and regulations of the board; (2) the chosen doctor or

hospital must render his services pursuant to these rules and regulations; and (3) the services or supplies must be furnished at uniform rates of compensation to be fixed by the board. But the board was expressly prohibited from entering into any exclusive contract for these services. The first board adopted plan number one for the rendition of medical services and rules and regulations to carry it into effect. A monthly deduction of \$2.50 was made and then came a suit to test the constitutionality of the legislation. The Supreme Court of California, with one judge dissenting, decided that the legislation was valid despite many objections such as delegation of legislative power, due process, equal protection, and religious freedom.¹⁶ It is hardly to be doubted that the court was happy to announce that the municipal employees had voted in favor of the system at the outset by a vote of 7,428 to 939 and that: "Over a thousand physicians, a majority of the licensed practitioners in the city, and nearly all of the city's hospitals, agree to furnish services under the plan. And petitioners' brief states that among those who have joined the staffs are the president of the State Board of Health, the president of the California State Medical Association and past presidents of that association, the president of the San Francisco County Medical Society and several past presidents of that society, the president of the American College of Physicians, and leading members of the staffs of the medical schools of the University of California and Stanford University." The uncertainty in this opinion is contained in the expression, "rules and regulations of the board." Until these rules and regulations are disclosed and discussed in a court opinion one cannot be sure of the scope of the opinion in *Butterworth v. Boyd*. But it would appear that the decision sustains the constitutionality of one type of group (socialized) medicine as distinguished from what may be labelled, inexactly, as the corporate practice of medicine.

A similar organization in California was known as California Physicians' Service, a non-profit corporation. The membership consisted of (1) administrative members who exercised administrative control through the election of the board of trustees; (2) professional members, duly licensed physicians and surgeons practicing in the state, who elected the administrative members periodically; and (3) beneficiary members, viz., those who upon the payment of monthly dues are entitled to secure from any professional member the necessary medical and surgical services. "Professional membership is open to any physician or surgeon licensed to practice his profession in this state upon his agreeing to abide by the rules of the corporation that all compensation for services rendered a beneficiary member shall be paid upon a pro rata basis out of the monthly funds collected from the beneficiary members." But a professional member could refuse to accept any person as a patient. It was stated by the corporation that approximately 5000 California physicians and surgeons were members and that 100,000 persons, increasing at the rate of 1500 per month, had become beneficiary members. Two years after the California Physicians' Service was incorporated, the California legislature passed an act applicable to the Service that

provided: (1) at least one fourth of all physicians and surgeons had to become members; (2) membership in such a non-profit corporation upon a uniform basis is available to all licensed members of a particular profession; and (3) voting by proxy and cumulative voting are prohibited. The California Physicians' Service was declared by the Court of Appeals, First District, to be validly operating under California laws and not to be engaging in the insurance business or in the corporate practice of medicine.¹⁷ In the opinion of the court is the following language: "There is no essential difference between the Group Health Association, the San Francisco Health Service, and California Physicians' Service in so far as the scheme of operations is concerned except that in the first two the administrative management is in a board selected by the beneficiary members, whereas in the latter it is in a board selected by the professional members. All are non-profit, semi-charitable organizations conducted for the primary purpose of affording necessary medical care to those of small income."

The above expression "Group Health Association" refers to the opinions in *Group Health Ass'n v. Moor* and *Jordan v. Group Health Ass'n*. The first of these two cases decided that the Group Health Association, organized in the District of Columbia, was not practising the healing art or engaged in the business of insurance in violation of law.¹⁸ The second case, in the Court of Appeals, affirmed this decision as to the second point only.¹⁹ No appeal was taken from the decision on the first point. From the two opinions these facts appear concerning the Group Health Association. It was organized as a non-profit corporation to provide its members and their dependents with medical services, surgery, hospitalization and medical and surgical supplies. There were specified exceptions and limitations on the services. Membership was limited to civil employees of the executive branch of the United States government service. Members were elected by the boards of trustees, who in turn were elected by the members except two chosen by the Federal Home Loan Bank Board, all from the membership. Members paid monthly dues and they could be expelled by the trustees who controlled and managed the corporate affairs. The relationship between the corporation and the physicians was not very clear. It had discontinued its former practice of having a staff of full-time salaried physicians in favor of a system whereby the physicians under oral contracts "apparently devote only a portion of their time to the work of Group Health, the remainder being devoted to private practice, although it seems to be contemplated that some physicians will give full time to the work. They receive fixed annual compensation, paid in monthly instalments, not specific fees for each treatment or case." It operated a clinic and provided for home treatment, if necessary. Hospitalization to a limited extent was secured by arrangement with independent established hospitals. But it does not appear that Group Health provided that any licensed practitioner who would abide by the rules and regulations was entitled to be on the panel approved by Group Health for calling by its members. This absent feature seems to be highly important

under the California decisions. The Court of Appeals was apparently not concerned with this fact since its task was to decide whether Group Health was in the insurance business. The decision of the District Court that Group Health was not practising the healing art was expressed in a brief opinion that did not consider this possible objection. It was the conclusion of the Court of Appeals that doctors who made contracts with Group Health were "independent contractors" required to exercise their own judgment entirely independently as to diagnosis and treatment.

This is an appropriate place to ask what is the essential difference between the Group Health Association in the District of Columbia, the California Physicians' Service, and the San Francisco health service system on the one hand and the Pacific Health Corporation and the United Medical Service in Illinois on the other hand? The best answer appears to be the profit motive with its danger of divided loyalty, intellectual dishonesty, and shoddy medical service. This is a sufficient differentiation on paper. Yet it seems fair to observe that a non-profit association cannot be wholly immune to expense, to making ends meet, and administrative success. And these are factors that will hamper and probably prevent the attainment of the high ideal of entirely adequate medical service for those with low incomes. So it is feared that in practice there would not be a great difference between approved non-profit corporations and disapproved profit corporations if the latter had been generally permitted to develop. Some of the latter probably would have developed into institutions with good if not excellent records for service. It can hardly be doubted, however, that many of them would have been of poor quality and even disgraceful. Thus would have arisen a need for public supervision and that, in an approved fashion, is not easy to obtain or cheap. Accordingly, the final conclusion is that the non-profit coöperative way is the superior method. If that method proves to be successful there will be little or no regret that the "practice of medicine" by the profit corporation has been generally forbidden.²⁰

PROCEDURAL DUE PROCESS

Not only is a physician entitled to substantive due process as set forth above, but he is entitled to procedural due process before his substantive rights can be adversely affected. Thus, the Ohio Supreme Court held that even though a statute provided that a license could not be revoked except upon notice and hearing, nevertheless it was unconstitutional because it failed to provide "whereby the attendance of witnesses could be required or their testimony procured."²¹

Missouri apparently was more careful than Ohio and provided by statute that testimony could be taken by deposition and used in the trial of a physician before the state board of health. Officers who take depositions were authorized to compel witnesses to attend and give their testimony. The Supreme Court of the United States held that this was sufficient for pro-

cedural due process even though the board had no power to compel witnesses to appear in person before the board and there give their testimony.²²

Perhaps the most colossal quack to disgrace the American medical profession was John R. Brinkley, the goat gland surgeon, who barely missed election as governor of Kansas, even though he ran on an independent ticket—a remarkable feat that was equally remarkable proof of the emotional gullability of too many Americans. After the State Board of Medical Registration and Examination of Kansas filed a complaint to revoke his license, Dr. Brinkley sought to enjoin the board from holding a hearing because, among other complaints, the board lacked the subpoena power. He failed to obtain an injunction.²³ The Kansas Supreme Court said that: “With the exception of a sporadic case to be noted later, no court has ever declared that [an] opportunity to present [a] defense and be heard in its support requires the adjective element of compulsory process.” The exceptional case mentioned by the Kansas court was the case decided by the Ohio Supreme Court. The Kansas Supreme Court was caustic in its adverse comment, viz.: “The decision is authority for nothing but the fact that it was rendered, and this court declines to follow it.”

In 1930 the Kansas board revoked Brinkley's license. Then Brinkley sought to enjoin this revocation, claiming that it denied him his rights under the national constitution. He was unsuccessful but he confronted the federal courts with a difficult decision.²⁴ His best argument was that the members of the Kansas Medical Board were prejudiced against him before the hearing started and that some of them were active in making the complaint against him. The Circuit Court of Appeals admitted “that some of the board had expressed such prejudice, and doubtless all were in fact prejudiced.” This conclusion was explained by the fact that Brinkley's methods of publicity, particularly the use of the radio, made previous knowledge of these facts and opinions concerning their violation of professional standards almost inevitable. Thus the court was confronted with a decision in favor of Brinkley, because the only body that could try him was disqualified by prejudice, or a decision adverse to Brinkley. In this unhappy dilemma the Circuit Court of Appeals chose not to let Brinkley go “Scot-free” and thus proclaimed that a doctor could not by sensational methods of publicity oust the only body with jurisdiction over him. And yet it is unfortunate for us to admit that a person had to be tried before a board that undoubtedly was prejudiced. Normally, courts could be expected to deny such a conclusion.²⁵

It is implied in the preceding discussion concerning procedural due process that before adverse action is taken against a medical man, he is entitled to a notice and a hearing. So is the law written²⁶; but it is also true that some courts have had an unfriendly attitude toward administrative tribunals and thus have been unnecessarily strict and legalistic in applying this sensible rule.²⁷

RESTRAINT OF TRADE

The American Medical Association and others were indicted for a conspiracy to restrain trade in violation of the Sherman Anti-trust Act. The Group Health Association of the District of Columbia was the alleged victim of the conspiracy. The District Court sustained demurrers to the indictment, holding that medical practice is not a trade within the meaning of Section three of the Sherman Act.²⁸ However, this decision was reversed and remanded by the Circuit Court of Appeals.²⁹ It held that "a restraint imposed upon the lawful practice of medicine—and a fortiori—upon the operation of hospitals and of a lawful organization for the financing of medical services to its members, is just as much in restraint of trade as if it were directed against any other occupation or employment or business." The opinion condensed the charge against the medical societies in this fashion: that they conspired to prevent the successful operation of Group Health's plan, and that the steps by which this was to be effectuated were as follows: "(1) to impose restraints on physicians affiliated with Group Health by threat of expulsion or actual expulsion from the societies; (2) to deny them the essential professional contacts with other physicians, and (3) to use the coercive power of the societies to deprive them of hospital facilities for their patients."³⁰ Upon the trial which followed, the American Medical Association and the Medical Society of the District of Columbia were convicted. They appealed but the convictions were affirmed, first, by the Circuit Court of Appeals for the District of Columbia and then by the Supreme Court.³¹ The latter court avoided a decision on the "question whether a physician's practice of his profession constitutes trade under § 3 of the Sherman Act." But it held that: "Group Health is a membership corporation engaged in business or trade. Its corporate activity is the consummation of the co-operative effort of its members to obtain for themselves and their families medical service and hospitalization on a risk-sharing prepayment basis. The corporation collects its funds from members. With these funds physicians are employed and hospitalization procured on behalf of members and their dependents. The fact that it is coöperative, and procures service and facilities on behalf of its members only, does not remove its activities from the sphere of business.

"If, as we hold, the indictment charges a single conspiracy to restrain and obstruct this business it charges a conspiracy in restraint of trade or commerce within the statute. As the Court of Appeals properly remarked, the calling or occupation of the individual physicians charged as defendants is immaterial if the purpose and effect of their conspiracy was such obstruction and restraint of the business of Group Health."

At the same time that the American Medical Association was before the courts, a case was decided in Kentucky that may present another problem in restraint of trade. Dr. Hughes was a competent and qualified surgeon with a long and successful experience and with no proof against him of un-

professional conduct. In 1939 the superintendent of the Good Samaritan Hospital wrote to Dr. Hughes that in order for the hospital to continue as an accredited hospital, it would be necessary for him to have the indorsement of the proper board of officers of the American College of Surgeons. Apparently, Dr. Hughes was justified in interpreting this letter as denying him the use of the operating room in the hospital unless he ceased to perform some types of operations. For the letter was based on the fact that Dr. Hughes, "a general practitioner, had invaded the field of the specialist by performing certain operations, which are under rules usually performed in the hospital by surgeons classified as specialists, and such continued practice would take the hospital from the accredited list." Dr. Hughes sought an injunction to restrain the hospital from interfering with his practice. An injunction was refused, the court saying: "We have before us merely one question—his vested right to operate in the rooms of appellee hospital, when it for no manifested arbitrary or capricious reason, but in the exercise of a reasonable discretion to maintain its institution on an accredited basis, decided otherwise. Appellant has failed to demonstrate that he has such a vested right, either by contract, inherently or as vouchsafed by any constitutional provision, hence we are of the opinion that the chancellor properly dissolved restraining order and denied permanent injunction." ³²

There was no discussion of the possibility that the arrangement between the hospital and the American College of Surgeons was an agreement in restraint of trade and a possible violation of the Sherman Act, to say nothing of Kentucky statutes. Was the arrangement one that can be diffentiated from the conduct condemned in the Group Health case because it is a reasonable restraint since the primary, if not the sole, purpose was to maintain proper standards for hospitals? The present writer is not sufficiently versed in the complications of the Sherman Act to venture an answer to this question.

COMPULSORY MEDICAL ATTENTION

Professor Thomas Reed Powell has written about the constitutional aspects of compulsory vaccination and sterilization. But he confined his observations to cases decided by the United States Supreme Court.³³

Not all of our state courts have been so favorably inclined toward the validity of compulsory medical treatment. The bulk of the litigation has concerned itself with vaccination against smallpox, as a condition of school attendance. As far as the writer is aware no state statute directly requiring such a vaccination has been held to be beyond the power of the state. But Illinois, not usually listed as politically and judicially progressive, has three cases in which a vaccination requirement was held to be invalid as beyond the delegated authority of the public body which attempted to enforce the requirement.³⁴ The mental obtuseness of these decisions is demonstrated to some extent by the opinion in a later Illinois case.³⁵ But even there the earlier decisions were distinguished because in the later case there was an

epidemic of smallpox, viz., about 40 cases in a city of approximately 12,000 population. Presumably there are those who can view with sweet tolerance the attitude of a supreme court that permitted the protection of vaccination only after the disease was a serious problem.³⁶ A Wisconsin decision fully supports the earlier Illinois decisions and more definitely condemned the vaccination regulation as unconstitutional.³⁷ Fortunately, however, it appears to be agreed that by one method or another most vaccination statutes and regulations have been held to be valid by the state courts, despite constitutional claims of equal protection, due process, non-delegation of legislative power, free public schools, religious and civil liberty, and freedom from unreasonable search and seizure.³⁸

There was difficulty in Illinois in securing a statute that compelled under a penalty the dropping into the eyes of a baby within an hour after its birth 1 per cent solution of silver nitrate, or some equally effective prophylactic. Even though the purpose was to save eye-sight by preventing the disease of ophthalmia neonatorum, the Attorney-General of Illinois wrote an opinion declaring the proposed statute to be unconstitutional for interfering with the liberty of parents in rearing their children. The Governor accordingly vetoed the bill.³⁹ But this ridiculous position was too much for Illinois. The next legislature passed another bill and it was approved by Governor Horner. As far as is known no court test has been made of such legislation.

In November, 1919, George Buckner was in custody in the Topeka, Kansas, city jail. The city health officer, acting under a state statute, the rules of the state board of health, and a Topeka ordinance, examined Buckner and then certified that he was infected with chronic gonorrhea. Then followed an isolation order whereby Buckner would be sent to the Kansas State Quarantine Camp for men at Lansing for treatment. Buckner sought his release through a writ of habeas corpus. He failed and the Kansas Supreme Court held that the legislation was valid.⁴⁰

New York in 1922 passed an act under which a "neglected" child was one whose parent refuses, when able to do so, to provide necessary medical, surgical, institutional, or hospital care for such child. The Children's Court had the power to order a child to be examined by a physician and whenever such a child appeared to be in need of medical or surgical care, to make an order for such treatment. Helen Vasko was brought before this court upon the petition of the Westchester County Society for the Prevention of Cruelty to Children. Medical examination disclosed that Helen, two years old, had a glioma of the retina of the left eye, which was permanently blind; that the growth was probably of a malignant nature and would increase until it filled the eyeball; that it would then burst through the eyeball and protrude between the lids; and that in all probability, if left to nature, it would follow the optic nerve into the brain, thus causing her death. An operation to remove the left eye was recommended with the advice that statistics show a cure in about 50 per cent of the cases. But Helen's parents refused to permit the operation, the mother saying that she would rather have the child

as she is now. "God gave her the baby and God can do what he wants." This attitude of the parents was thought by the New York court to be arbitrary. Accordingly, the statute was held to be constitutional and the order adjudging the child to be neglected was affirmed. As a necessary inference from the opinion the trial court's order included a direction that the operation be performed and this was also approved.⁴¹

Patricia Hudson presented a sad case. She had a congenital deformity consisting of an abnormal growth of her entire left arm which made that arm much longer and larger than the right arm and rendered it absolutely useless. The minority of the court from an examination of a photograph concluded that the left arm was ten times the size of the other arm and nearly as large as her body. The medical testimony was that Patricia appeared to be frail; that she will remain in a rather weakened condition, an easy prey for infection; that her heart is burdened by reason of having to pump blood through the large left arm; and that her chest and spine are becoming deformed from carrying the enormous weight. Both physicians concluded that there was no remedy except amputation which they recommended, even though "there is a fair degree of risk of life involved in the operation." Patricia came before a juvenile court on the complaint of an adult sister that Patricia was not receiving needed medical care. Patricia was then 11 years old. Her brothers and sisters testified that Patricia's deformed arm made her shy and sensitive and deprived her of a normal life. She did not attend school because other children jeered at her. Patricia apparently did not testify but she frequently cried and stated that she wished to have her left arm removed. Three of her sisters testified that they favored the amputation even though they realized that Patricia might not survive the operation. Her father was an invalid and a weak character. He testified that he would not object to the amputation and also stated: "I am leaving it in the Judge's hands." Her mother strongly opposed the operation, not because of religious scruples, even though she had had a divine healer for Patricia, but because of the danger of causing Patricia's death.

The trial judge ordered the amputation but the Washington Supreme Court by a vote of six to three reversed the order.⁴² The majority opinion stated that the legal problem presented was whether Patricia's mother could be deprived of the control of Patricia for a sufficient period of time to subject Patricia to the operation which, in the judgment of the juvenile court, Patricia's welfare demanded.

The answer to this question was in the negative. Was it correct? One cannot give a negative answer to this last question without admitting that the Washington statute was in no sense as satisfactory and direct as the New York statute previously considered. Indeed it seems necessary to admit that the Washington juvenile court act was not drafted with any such problem specifically in mind. It has no express language providing for medical or surgical care. But it defined a dependent child as one who is destitute, or whose home, by reason of the neglect of a parent, is an unfit place for such

child, or one whose parent does not properly provide for such child, etc. The minority opinion argued that this language was sufficient and came to these conclusions: (1) "Medical services are necessary and a child who is not furnished such services is destitute;" and (2) since Patricia was in need of surgical attendance she was destitute and the juvenile court possessed the power to order the amputation.

In reaching these conclusions the minority relied on that part of the act which declared: "After acquiring jurisdiction over any child, the court shall have power to make . . . any order, which in the judgment of the court, would promote the child's health and welfare." The majority of the court appeared not to attach much value to this provision. Instead, it argued that under the same section, if the juvenile court found a child to be dependent, it was necessary to place the child under the legal control of somebody. "But the court may not, over objection of the natural guardian, or legal guardian or adoptive parents to whom custody and control of the child are awarded by the court, subject the child to a surgical operation."

Thus it is possible that the decision is primarily procedural in its significance. Instead of directly ordering the amputation, the juvenile court should have proceeded thus: (1) made a finding that Patricia was a neglected child under the statute; (2) made an order depriving her mother and father of her control and custody, taking care to have them transferred to a person, such as one of the adult sisters, who favored the amputation; (3) entertained a petition from this guardian asking for an amputation order, and; (4) made an amputation order in granting this petition. Whether this procedure would have been approved by the Supreme Court of Washington is doubtful. Despite the command of the legislature to give the juvenile court act a liberal construction, the majority of the court apparently failed to do so, or to heed the legal philosophy expressed by the New York court in the *Rotkowitz* case, even though it quoted this passage: "The law is a growth. It could not serve the purposes of man and his needs were it static, inflexible and rigid. Like life, the law constantly undergoes change—change which is imposed by life upon law."⁴³ In the course of an unnecessarily long opinion there is one paragraph in the Washington opinion that probably explains, beyond any merely logical setting forth of its reasons, the basic philosophy or perhaps the religious prejudice of the majority of the Washington court. It is worth quoting:

"As we read the evidence it is admitted by all concerned that there is a grave possibility that the child may not survive the ordeal of amputation; nevertheless, every one except the child's mother is willing, desirous, that the child be required to undergo the operation. Implicit in their position is their opinion that it would be preferable that the child die instead of going through life handicapped by the enlarged, deformed left arm. That may be to some today the humane, and in the future it may be the generally accepted, view. However, we have not advanced or retrograded to the stage where, in the name of mercy, we may lawfully decide that one shall be deprived of life

rather than continue to exist crippled or burdened with some abnormality. That right of decision is a prerogative of the Creator." This language, particularly the last sentence, reminds one of the excuse given by the mother of Helen Vasko in one of the New York cases. It was an excuse that the New York court thought was arbitrary. It is also odd that the majority of the Washington court criticized Patricia's mother, "who loves her child devotedly" for seeking "to shift responsibility of decision to the child at some future time, a present responsibility of the mother, a sacred duty the mother shirks." In any event it appears clear that despite a few vague references to constitutional rights, the Washington court did not decide Patricia's case on the theory that some principle of constitutional law would prevent the Washington legislature from amending its juvenile court act to conform to the New York acts. But it is regrettable that the majority of the Washington Supreme Court decided in favor of a static rather than a progressive view.

ENFORCEMENT OF STANDARDS

The normal method of compulsion if a person practises medicine or surgery without securing a license or after his license has been revoked or suspended is through a criminal proceeding with a jury trial. This method has not always been adequate. The statutory penalty may be so mild that it fails to deter some hardy individuals. More often, it seems, some quacks have a popular appeal and it is difficult if not impossible to convict them before a jury with sufficient frequency.

Iowa passed a statute that provided that a person who violated a law requiring a license for the practice of his profession could be restrained by a permanent injunction. This was in addition to a statute that made a medical practitioner subject to a fine and imprisonment for practising without a license. G. E. Fray became the defendant in an action to enjoin him from practising without a license. He complained that the first Iowa statute was unconstitutional because it deprived him of a jury trial as guaranteed by the Iowa constitution. But the Supreme Court ruled against him. The importance of this decision lies in the fact that an equity rather than a law court issues an injunction and that an equity court is not compelled to call a jury to determine the facts and very rarely does so. The assumption is that an equity judge has a higher I.Q. than the average jury, knows better from his experience how to evaluate evidence, and is less subject to prejudices and emotions. It is believed that quacks have less chance of avoiding the license law if the case is decided without a jury. In case the injunction issues, a claimed violation of the injunction decree will again be decided by the equity judge without the necessary use of a jury, unless a statute so requires. This method of enforcement of professional standards is also likely to be more speedy than a criminal proceeding. The Iowa Supreme Court admitted that this method could not be used in the ordinary prosecution of crimes. But for a long time equity courts have asserted jurisdiction over nuisances and

certain harms to property. Here the Iowa court made use of these analogies in favor of the public health and refused to hold the Iowa statute unconstitutional.⁴⁴ Other states have reached the same result and some of them have done so without the aid of a statute like the Iowa statute.⁴⁵ Still other states have refused to grant injunction decrees, holding that the criminal process would have to suffice.⁴⁶ In the last group of states three of the four cases concerned chiropractors. In the Illinois case it was asserted by the attorney general that some of the 52 individual defendants had been tried, convicted, and sentenced; that after paying their fines or serving their terms of imprisonment they returned and continued their practice, and that the Universal Chiropractors' Association collected dues from its members and paid all fines, costs, and attorneys' fees, thus creating disrespect for the law which makes it unlawful to treat human ailments without a license.

LIMITATIONS ON MEDICAL PRACTICE

Dr. Samuel W. Lambert, "a distinguished physician" in 1922 in New York, sought to enjoin a federal prohibition director from interfering with his practice of prescribing vinous or spirituous liquors to his patients for medical purposes. The director was acting under congressional statutes which strictly limited the amount of liquor which physicians could prescribe. Dr. Lambert claimed that his constitutional right as a physician had been infringed even though, according to the majority of the court, he belonged to the minority group of physicians, who believed that liquor had value as a therapeutic agent. A bare majority of the Supreme Court of the United States decided that the statutes were not arbitrary. Accordingly Dr. Lambert was denied judicial relief.⁴⁷ The minority of the court challenged the assertion by the majority of the court that the views of the medical profession concerning vinous and spirituous, as distinguished from malt, liquors were opposed to their use as medicine. The minority of the court, accordingly, proceeded on the premise that vinous and spirituous liquors are of medical value.

*Linder v. United States*⁴⁸ should be contrasted with the Lambert case. Dr. Linder sold to a known female addict one morphine tablet and three cocaine tablets. His expectation was that the addict would administer them to herself in divided doses over a period of time. Nevertheless, he was convicted of violating the Harrison Narcotic Law. This conviction was affirmed by the Circuit Court of Appeals but was reversed and remanded by the Supreme Court. It is difficult to interpret the decision and opinion of the latter court. The opinion hardly seems justified in assuming "the doctor's good faith" and the wisdom of his action according to medical standards. It would appear that the decision resulted from the following factors: (1) it was a trivial case; (2) the Supreme Court has been closely divided as to the constitutionality of the Harrison Narcotic Law; and (3) it was announced that the law, a taxing act with penal provisions, must be

strictly construed. The court also announced that "direct control of medical practice in the states is beyond the power of the federal government." On the whole it is believed that the Linder case is of no particular importance as a precedent.

CONTRACEPTIVES

There appears to be no doubt that the dispensing of contraceptives may be prohibited generally. To what extent, however, may physicians be compelled to accept such a prohibition? On the basis of the decided cases no final answer to this question will be ventured.⁴⁹ But it seems fair to observe that at least two recent decisions are unfavorable to the asserted constitutional right of physicians to prescribe the use of contraceptives even though they honestly believe that the use of contraceptives is desirable or necessary to protect the patient's health or life. Under this sort of a decision it would seem to follow that the patient has no constitutional right to have a physician advise him as to the necessity of using a contraceptive.

The first of these two decisions is *Commonwealth v. Gardner* which affirmed the conviction of a physician, a nurse, and two trained social workers. All worked for the North Shore Mothers' Health Office, a charitable organization. Two of them worked without pay and the contraceptive devices and medicine were sold and given in the office in accordance with the physician's instructions. No question was made concerning the physician's good faith. That seemed to be assumed. Despite that, the ruling of the trial court that these facts constituted no defense was approved. It was also held that the Massachusetts statute, prohibiting the dispensation of contraceptives, must be interpreted without qualification as applicable to physicians, and that, so interpreted, it was constitutional.⁵⁰ The Supreme Court of the United States blasted the appeal in this case by a dismissal "for the want of a substantial federal question." Nothing more was said and that would seem to be the equivalent of saying that the Supreme Court agreed with the Massachusetts court that the state statute as applied did not violate the national constitution, including the due process clause.⁵¹

Connecticut had a similar statute. Wilder Tileston, a licensed physician, sought a declaratory judgment to determine whether he was entitled to prescribe contraceptives for married women living with their husbands in the following cases: (1) patient is suffering from high blood pressure; if pregnancy occurred there would be imminent danger of toxemia of pregnancy which would have a 25 per cent chance of killing her; (2) patient is suffering from an arrested case of tuberculosis of the lungs of an acute and treacherous type so that if she should become pregnant such condition would be likely to light up the disease and set back her recovery for several years, and might result in her death; (3) patient is in good health except insofar as she has been weakened by having had three pregnancies in about 27 months and a new pregnancy would probably have a serious effect upon her general health and might result in permanent disability. Despite the ap-

pealing nature of these cases the Supreme Court of Connecticut decided that the statutes forbade Dr. Tileston from prescribing contraceptives for these patients even though that was his professional judgment. It also decided that the statutes, as interpreted, were constitutional.⁵² Why? Because a physician in such cases need not prescribe contraceptives. All he needs to do is to advise his patients to refrain from sexual intercourse for the duration. Observe this language of the court: "The claim of the state on this point comes down, then, to a consideration of whether abstinence from intercourse is a reasonable and practicable method of preventing the unfortunate consequences. Certainly it is a sure remedy. Do the frailties of human nature and the uncertainties of human passions render it impracticable? That is a question for the legislature, and we cannot say it could not believe that the husband and wife would and should refrain when they both knew that intercourse would very likely result in a pregnancy which might bring about the death of the wife." Would and should! The will and the morality! This writer does not believe that either the will or obedience to the moral precept will exist in many instances. And he is inclined to believe that this significant restriction on freedom of belief and action, based upon a lack of realism as to sexual relations, would be better condemned as unconstitutional.

The Connecticut decision was appealed to the United States Supreme Court. Its decision was narrowly confined to a point of procedure. Curiously the attorneys for Dr. Tileston had raised in the Connecticut court only the question whether the statutes deprived "any person of life without due process of law." The Supreme Court of the United States held that "the proceedings in the state courts present no constitutional question which appellant has standing to assert. * The sole constitutional attack upon the statutes under the Fourteenth Amendment is confined to their deprivation of life—obviously not appellant's [Tileston's] but his patients'. There is no allegation or proof that appellant's life is in danger. His patients are not parties to this proceeding and there is no basis on which we can say that he has standing to secure an adjudication of his patients' constitutional right to life, which they do not assert in their own behalf. * * * * No question is raised in the record with respect to the deprivation of appellants' liberty or property in contravention of the Fourteenth Amendment." ⁵³

NOTES

1. 272 U. S. 581, 47 S. Ct. 210 (1926).
2. For the benefit of the medical profession it is perhaps desirable to state that the term police power is just one way of expressing the idea that is better expressed by the words, regulatory power. Sometimes this regulatory power can be extended to a prohibition.
3. 129 U. S. 114, 9 S. Ct. 231 (1889).
4. *Reetz v. Michigan*, 188 U. S. 505, 23 S. Ct. 390 (1903); *Watson v. Maryland*, 218 U. S. 173, 30 S. Ct. 644 (1910—due process and equal protection); *Collins v. Texas*, 223 U. S. 288, 32 S. Ct. 286 (1912—osteopathy); *Crane v. Johnson*, 242 U. S. 339, 37 S. Ct.

- 176 (1917—drugless practitioner); *Douglas v. Noble*, 261 U. S. 165, 43 S. Ct. 303 (1923—dentists); *Graves v. Minnesota*, 272 U. S. 425, 47 S. Ct. 122 (1926—dentists; see citation of many state decisions); *Sage-Allen Co. v. Wheeler*, 119 Conn. 667, 179 Atl. 195, 98 A. L. R. 897 (1935—optometry). Cf. *People v. Griffith*, 280 Ill. 18, 117 N. E. 195 (1917—Act of 1915 to regulate optometry invalid).
5. *Meffert v. Packer*, 66 Kan. 710, 72 Pac. 247, 1 L. R. A. N. S. 811 (1903); *Richardson v. Simpson*, 88 Kan. 684, 129 Pac. 1128, 43 L. R. A. N. S. 911 (1913—dentist); *Laughney v. Maybury*, 145 Wash. 146, 259 Pac. 17, 54 A. L. R. 393 (1927—advertising); *Yoshizawa v. Hewitt*, 52 F. (2d) 411, 79 A. L. R. 317 (1931); *State Dental Examiners v. Savelle*, 90 Colo. 177, 8 Pac. (2d) 693, 82 A. L. R. 1176 (dentist practicing as employee of a corporation).
 6. *Green v. Blanchard*, 138 Ark. 137, 211 S. W. 375, 5 A. L. R. 84 (1919—dentist—divided court).
 7. *Laughney v. Maybury*, 145 Wash. 146, 259 Pac. 17, 54 A. L. R. 393 (1927); *McNaughton v. Johnson*, 242 U. S. 344, 37 S. Ct. 178 (1917); *People v. Witte*, 315 Ill. 282, 146 N. E. 178, 37 A. L. R. 672 (1924).
 8. *Louisiana State Bd. of Medical Examiners v. Fife*, 162 La. 681, 111 So. 58, 54 A. L. R. 594 (1926). While not precisely the same it appears impossible to reconcile satisfactorily with the Louisiana case, *People v. Love*, 298 Ill. 304, 131 N. E. 809, 16 A. L. R. 703 (1921) and *People v. Schaeffer*, 310 Ill. 574, 142 N. E. 248 (1924).
 9. *People v. Lewis*, 233 Mich. 240, 206 N. W. 553 (1925—Michigan recognized chiropractors but held that one desiring to practice the system of chiropractic is not deprived of the equal protection of the laws by requiring him, as a condition for securing a license, to pass an examination in anatomy, histology, embryology, physiology, chemistry, bacteriology, pathology, diagnosis, hygiene, and public health, although such subjects are not taught in chiropractic schools).
- The board of regents of Texas University leased land to the city of Galveston for a municipal hospital, reserving the right to use part of the hospital for clinical instruction of university medical students. The hospital board in charge of the hospital excluded licensed osteopathic physicians from using this hospital. But this was held to be no violation of due process or equal protection. *Hayman v. City of Galveston*, 273 U. S. 414, 47 S. Ct. 363 (1927—"We cannot say that a regulation excluding from the conduct of a hospital the devotees of some of the numerous systems or methods of treating diseases authorized to practice in Texas, is unreasonable or arbitrary.")
- See for a more general discussion of equal protection, *Iowa Ec. Med. College Ass'n. v. Schrader*, 87 Ia. 659, 55 N. W. 24, 20 L. R. A. 355 (1893).
10. *State ex rel. Walker v. Green*, 112 Ind. 462, 14 N. E. 352 (1887); 136 A. L. R. 219 (Annotation). See, also, *Fairfield v. Shellenberger*, 135 Ia. 615, 113 N. W. 459 (1907—special license tax on traveling physicians). Cf. *State v. Doran*, 28 S. D. 486, 134 N. W. 53 (1912 occupation tax applicable only to non resident itinerant physicians invalid).
 11. *State v. Luscher*, 157 Minn. 192, 195, N. W. 914 (1923).
 12. *York v. State*, 144 Fla. 216, 197 So. 766 1 Loyola L. Rev. 109 (1940—It is not clear whether the peremptory writ of mandamus required the board to produce the examination papers of June 1939 in order to determine whether relator's grade entitled him to a certificate or whether it required the board to issue the certificate forthwith).
 13. *Semler v. Oregon State Board of Dental Examiners*, 294 U. S. 608, 55 S. Ct. 570 (1935).
 14. *People by Kerner v. United Medical Service*, 362 Ill. 442, 200 N. E. 157, 103 A. L. R. 1229 (1936). The opposite ruling was made in New York as to a chiropodist: *People v. Dr. Scholl's Foot Comfort Shops, Inc.*, 277 N. Y. 151, 13 N. E. (2d) 750 (1938).
 15. 12 Cal. (2d) 156, 82 P. (2d) 429, 119 A. L. R. 1284 (1938).
 16. *Butterworth v. Boyd*, 12 Cal. (2d) 140, 82 P. (2d) 434, 126 A. L. R. 838 (1938).
 17. *California Physicians' Service v. Garrison*, Cal. App. 155 P. 2d 885 (1945).
 18. *Group Health Ass'n v. Moor*, 24 F. Supp. 445 (1938).

19. *Jordan v. Group Health Ass'n.*, 107 F. 2d 239 (1939). See, however, *U. S. v. American Medical Ass'n.*, 110 F. 2d 703 (1940) where the Circuit Court of Appeals was unable to say that the Group Health Association, Inc., as described in the indictment before the court, was illegally practising medicine.
20. See the opinion in *U. S. v. American Medical Ass'n.*, 110 F. 2d 703, 714 (1940). Contrast 27 Marq. L. Rev. 135 (1943).
21. *Jewell v. McCann*, 95 Ohio St. 191, 116 N. E. 42 (1917).
22. *Missouri ex rel. Hurwitz v. North*, 271 U. S. 40, 46 S. Ct. 384 (1926).
23. *Brinkley v. Hassig*, 130 Kan. 874, 289 Pac. 64 (1930).
24. *Brinkley v. Hassig*, 83 F. (2d) 351 (1936).
25. Disqualification on the Ground of Bias as Applied to Administrative Tribunals, 23 The Canadian Bar Rev. 453 (1945); *Re Segal and Smith*, 5 Fed. C. C. Rep. 3 (1937).
26. *State v. Schultz*, 11 Mont. 429, 28 Pac. 643 (1892).
27. *Dymment v. Board of Medical Examiners*, 57 Calif. App. 260, 207 Pac. 409, 412 (1922); *Bley v. Board of Dental Examiners*, 120 Calif. App. 426, 7 P. 2d 1053 (1932); *Kalman et al. v. Walsh et al.*, 355 Ill. 341, 189 N. E. 315 (1934); *Abrams v. Jones*, 35 Ida. 532, 207 Pac. 724 (1922).
28. *U. S. v. American Medical Ass'n.*, 28 F. Supp. 752 (1939).
29. *U. S. v. American Medical Ass'n.*, 110 F. 2d 703 (1940). See *The Medical Profession and the Sherman Act*, 8 Geo. Wash. L. Rev. 1034 (1940).
30. *Ibid.*, at p. 711.
31. *American Medical Ass'n. v. U. S.*, 130 F. 2d 233 (1942), 317 U. S. 519, 63 S. Ct. 326 (1943). See comments in 29 Corn. L. Qu. 271 (1943); 29 V. L. Rev. 832 (1943), 18 Tenn. L. Rev. 393 (1944).
32. *Hughes v. Good Samaritan Hospital*, 289 Ky. 123, 158 S. W. (2d) 159 (1942), reviewed in 31 Ky. L. Jr. 197 (1943).
33. *Compulsory Vaccination and Sterilization: Constitutional Aspects*, 21 N. C. L. Rev. 253 (1943).
34. *Potts v. Breen*, 167 Ill. 67, 47 N. E. 81 (1897—A rule of State Board of Health compelling vaccination of school children is unreasonable and beyond the power of the board where smallpox does not exist in the community and there was no reason for apprehension); *Lawbaugh v. Board of Education*, 177 Ill. 572, 52 N. E. 850 (1899); *People v. Board of Education*, 234 Ill. 422, 84 N. E. 1046 (1908).
See also *Burroughs v. Mortenson*, 312 Ill. 163, 143 N. E. 457 (1924) and *People v. Tait*, 261 Ill. 197, 103 N. E. 750 (1913).
35. *Hagler v. Lerner*, 284 Ill. 547, 120 N. E. 575 (1918).
36. The decision and the attitude of the Supreme Court of Illinois was much better in *People ex rel. Barmore v. Robertson*, 302 Ill. 422, 134 N. E. 815 (1922). There it was held that a typhoid carrier had been legally placed under a quarantine which required her to remain in her home and forbade her to prepare food for anyone except her husband and forbade anyone to come into her home, as a roomer or otherwise, unless he had been immunized from typhoid fever.
37. *State ex rel. Adams v. Burdge*, 95 Wis. 390, 70 N. W. 347 (1897). See a criticism of the Burdge case in *Ex parte Company*, 106 Oh. St. 50, 59, 139 N. E. 204 (1922).
38. *Hartman v. May*, 168 Miss. 477, 151 So. 737, 93 A. L. R. 1408 (1934). See also *Zucht v. King*, 260 U. S. 174, 43 S. Ct. 24 (1922).
39. See an editorial in 26 Ill. L. Rev. 785 (1932). *People v. Pierson*, 176 N. Y. 201, 68 N. E. 243 (1903) holds that a statute that makes it a misdemeanor wilfully to omit medical attendance for an adopted child did not violate the father's constitutional freedom of religion even though he believed in divine healing and not in physicians. See also *Owens v. State*, 6 Okla. Cr. Rep. 110, 116 Pac. 345 (1911).
40. *Ex Parte McGee*, 105 Kan. 574, 185 Pac. 14, 8 A. L. R. 831 (1919). See also *People v. Thomas*, 231 N. Y. S. 271, 133 Misc. Rep. 145 (1928—detention for blood test); *In re Caselli*, 62 Mont. 201, 204 Pac. 364 (1922); *Ex parte Company*, 106 Oh. St. 50,

139 N. E. 204 (1922) ; In re Travers 48 Cal. App. 764, 192 Pac. 454 (1920). Contrast *Wragg v. Griffin*, 185 Ia. 243, 170 N. W. 400 (1919) which appears to be a reactionary decision.

41. In re Vasko, 263 N. Y. S. 552, 238 App. Div. 128 (1933). This decision was the subject of comment in 12 Tenn. L. Rev. 59 (1933) ; 14 Boston U. L. Rev. 196 (1934) ; 28 Ill. L. Rev. 556 (1933).

In re Rotkowitz, 25 N. Y. S. 2d 624, 175 misc. 948 (1941) is a similar decision upon an order for an operation to correct and prevent extension of a leg deformity induced by poliomyelitis. The mother of the child petitioned for the order and the court found that the child was neglected by the father who would not consent to the operation. He gave no reason for his opposition.

42. In re Hudson, 13 Wn. (2d) 673, 126 P. 2d 765 (1942). The comment on this decision in 28 Ia. L. Rev. 372 (1943) is mildly critical: "Even in the absence of statute, the state's right of guardianship is superior to that of the parent if the assertion of the right is necessary for the welfare of the child. This authority should extend to an order for surgical care in a proper case."
43. 25 N. Y. S. 2d 624, 175 Misc. 948 (1941).
44. State v. Fray, 214 Iowa 53, 241 N. W. 663, 81 A. L. R. 286 (1932). See Legal Control of Medical Charlatanism, 22 N. C. L. Rev. 23 (1943) discussing and comparing the use of criminal prosecution, quo warranto, and injunction.
45. State ex rel. La Prade v. Smith, 43 Ariz. 131, 29 P. (2d) 718, 92 A. L. R. 168 (1934).
46. Dean v. State ex rel. Anderson, 151 Ga. 371, 106 S. E. 792 (1921) ; Redmond v. State ex rel. Attorney General, 152 Miss. 54, 118 So. 360 (1928—recommendation that state proceed by information to abate nuisance with a jury trial) ; State v. Maltby, 108 Neb. 578, 188 N. W. 175 (1922) ; People v. Chiropractors Ass'n., 302 Ill. 228, 134 N. E. 4 (1922).
47. Lambert v. Yellowley, 272 U. S. 581, 47 S. Ct. 210, 49 A. L. R. 575, 588 (1926).
Early Legislation Regulating The Practice of Medicine in 18 Ill. L. Rev. 225 (1923) is of general interest.
48. 268 U. S. 5, 45 S. Ct. 446 (1925).
49. See McConnell v. Knoxville, 172 Tenn. 190, 110 S. W. (2d) 478, 113 A. L. R. 966 (1937).
50. Commonwealth v. Gardner, 300 Mass. 372, N. E. 2d 222 (1938) ; 6 U. of Chic. L. Rev. 260 (1939) is critical of this decision. See also 50 Yale L. Jr. 682 (1941) ; 37 Mich. L. Rev. 317 (1938) ; 7 George Washington L. Rev. 255 (1938) ; 16 N. Y. U. L. Qu. Rev. 149 (1938).
51. Gardner v. Commonwealth of Massachusetts, 305 U. S. 559, 59 S. Ct. 90 (1938).
52. Tileston v. Ullman, 129 Conn. 84, 26 A. 2d 582 (1942). Two of the five judges dissented on the interpretation of the statute ; but they said nothing about its constitutionality.
See 20 Boston U. L. Rev. 551 (1940) ; 3 Univ. of Det. L. Jr. 216 (1939).
53. Tileston v. Ullman, 318 U. S. 44, 63 S. Ct. 493 (1943).

CASE REPORTS

PULMONARY FILARIASIS *

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FILARIASIS, a disease formerly of interest to tropical medical practitioners, has become a problem which must now be recognized and managed by both medical officers and civilian physicians. Early in the war the disease was contracted by certain groups of American troops serving duty in filarial endemic areas in the South Pacific. Since the vector host is present in many areas in the Central Pacific, a continued incidence of the disease among our troops is a possibility. It seems important, therefore, to note all the clinical variants of the disease. The pathological findings, as manifested in natives, have been carefully worked out by Manson-Bahr¹ and O'Connor.² Essentially, there is lymph stasis and edema of the lymphatics associated with the presence of worms within the lumen. As the disease progresses, these foci undergo necrosis, with eosinophilic cellular infiltration of lymphatic wall. Eventually, there may be disintegration and calcification of the parasites, with peripheral infiltration of the lymphatic walls with macrophages, giant cells, lymphocytes, plasma cells, and fibroblasts. It is common opinion that the obstruction of lymph tracts produced by the tissue reaction surrounding the dying and dead worms accounts for the later picture of elephantiasis. The underlying morphological findings of early filariasis in American troops has been recently described by Michael,³ Rifkin and Thompson,⁴ Zuckerman and Hibbard,⁵ and Wartman.⁶ In all these series, there is distinct evidence of macrophagic proliferation, with fibroblastic overgrowth, and eventual fibrous obliteration of the involved lymphatics.

It is believed by many that a systemic reaction occurs either as a result of an allergic or a toxic reaction to breakdown of the worms. It has been possible to demonstrate that this acute hyperergic reaction may occur throughout the body, and is manifested by eosinophilia, edema, and hyperplasia of lymph nodes or edema and eosinophilic infiltration of the lymphatic walls. This may occur in areas far removed from the primary focus. It has been possible for us, in cases of suspected filariasis, to examine by biopsy the axillary and epitrochlear lymph nodes and lymphatics, when the primary focus appeared to be the right or left paminiform plexus. These para-focal nodes revealed lymph stasis, hyperplasia, and eosinophilia.

The sequelae of these progressive changes are usually increased intraluminal tension, with rupture of the lymphatics concerned, and spillage of lymph fluid into one of the organ or serous cavities. Craig and Faust⁷ describe chyluria, secondary to ruptured lymphatics of the bladder or kidney. Strong⁸ mentions chylocele developing as a result of increased tension, with rupture of the lymphatics of the tunica vaginalis. He further makes note of the fact that occa-

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sionally microfilariae are found in blood-stained sputum. He makes no mention of this phenomenon with associated pulmonary findings. In a recent editorial in the Naval Medical Bulletin,⁹ a statement is made that "there is a pulmonic phase (in filariasis) manifested by a prevalent morning cough, (so) conspicuous in natives of endemic areas, which leads to a suspicion of widespread tuberculosis." This is noted as an example of the protean character of the disease. It has not been possible to find in the literature at hand recorded cases of proved pulmonary filariasis or filarial pneumonia.

We have recently had occasion to examine a South Pacific native who had been infected with filariasis (*W. bancrofti*) and whose clinical picture suggests the possibility of pulmonary filariasis.

CASE REPORT

The patient was a 39-year old civilian laborer, who was a native from a South Pacific island where filariasis is endemic. With the exception of the latter three years



FIG 1 December 2, 1943 Soft, diffuse shadow in left lower lobe and small ill-defined shadow in right upper lobe

of his life, he had always lived on this island. He was admitted to a general hospital in the South Pacific region, having been transferred from a station hospital, because of hacking cough, expectoration of blood-stained sputum, and night sweats, of two years' duration. He complained of fatigue and malaise. No other symptoms referable to any other system were noted. Physical examination revealed an afebrile individual, of good build, who did not appear to be acutely ill. On admission, temperature was 98.8° F; pulse 80 per minute; respirations 24 per minute; blood pressure

110 mm. Hg systolic and 70 mm. diastolic. Dullness, diminished breath sounds, and moist râles were noted in the right half of the chest, anteriorly and posteriorly and below the angle of the scapula on the left side, posteriorly. Lymphadenopathy was not present. There was no evidence of elephantiasis of the upper or lower extremities. The remainder of the physical examination was essentially negative. Admission diagnosis was tuberculosis, chronic, non-productive, moderately advanced.

Roentgenographic Examination: A film of the chest from another hospital taken December 2, 1943 (figure 1) showed a soft mottled diffuse shadow of increased density



FIG 2 January 16, 1944. The shadow in the right upper lobe has extended to almost the entire upper lobe and both shadows have become hard and linear.

fanning out from the left hilum into the lower lobe, and covering the lung field from the border of the eighth rib downward. The shadow became less dense below and laterally, leaving the lung margins almost clear. A shadow of the same character, but occupying an irregular localized area about 5 cm. in diameter, lay in the mid-zone of the right second anterior interspace. Heavy dense trunk markings connected this shadow with the hilum. The broncho-vascular markings were prominent throughout the lung fields.

A second transfer film, dated December 20, 1943, showed slight regression of the shadow in the left lower lobe, more contrast to the mottling, and beginning hard linear markings in the shadow on the right side. The small patch on the right had developed into a generalized fluffy density covering the entire lung field below the level of the anterior end of the third rib.

Our film (figure 2) taken on January 16, 1944, revealed marked regression of all of the shadows. The fluffy shadows of parenchymal infiltration had cleared, leaving in the left lower and right upper lobes rather fan-shaped zones of hard linear densities extending from the hila for varying distances into the lung fields.

Laboratory Data: The admission blood count revealed 4,450,000 red blood cells, 7,800 white blood cells, 92 per cent hemoglobin, 44 per cent neutrophils, 25 per cent

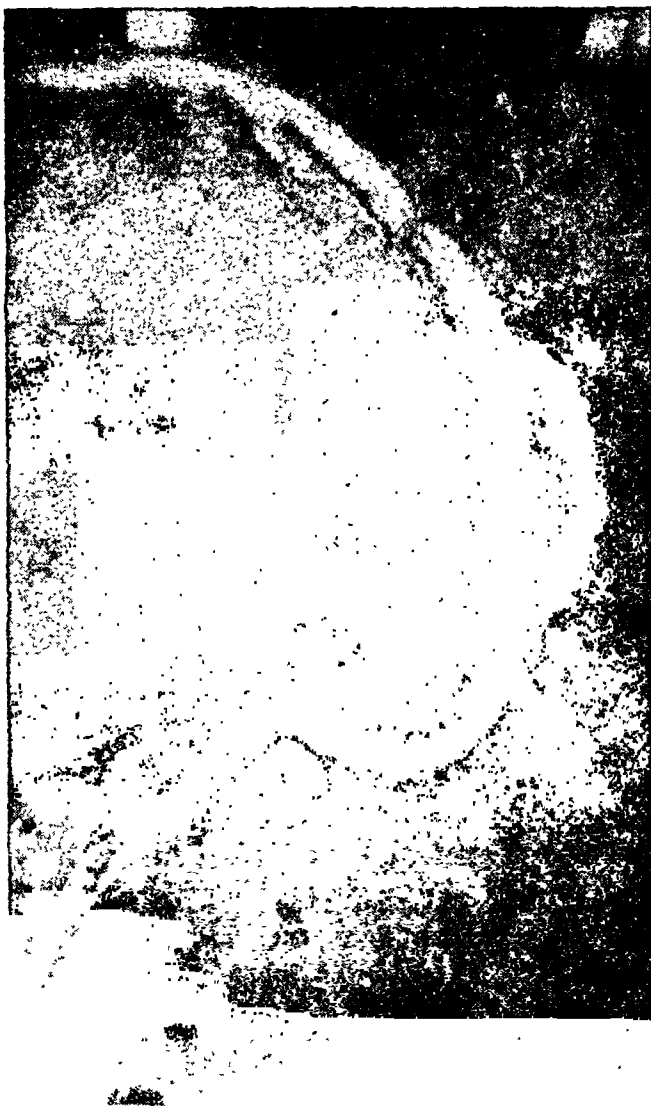


FIG. 3. Microfilaria in sputum smear (*W. bancrofti*). $\times 600$.

lymphocytes, 28 per cent eosinophiles, 3 per cent monocytes; urine examination was negative; Kahn reaction was negative; malaria smears on four occasions revealed no plasmodium; sedimentation rate was 51 mm. (Wintrobe); examinations of four separate sputum concentrates revealed no acid fast bacilli; there was no evidence of yeasts, fungi, or molds. However, numerous microfilariae, characteristic of *Wuchereria bancrofti* were noted (figure 3). These were associated with many eosinophiles. Peripheral blood examination by the Knott concentration method¹⁰ revealed a heavy

microfilarial infestation. A skin test,¹¹ utilizing *Dirofilaria immitis* antigen, gave a positive reaction to a titer of 1:8000 and 1:16000. Tuberculin test (PPD) was positive in a dilution of 1:10000. Because of the high eosinophile count, stool examinations were performed, and revealed many hookworm ova (type unidentified). "Cold agglutinin" studies were negative. A blood count repeated one week following admission revealed 8,400 white blood cells with 31 per cent eosinophiles. Otherwise no changes were noted. Sedimentation rate, one week after admission, revealed a drop to 40 mm. in one hour. Sputum cultures on two occasions revealed non-hemolytic streptococci.

COMMENT

The clinical findings, the serial roentgenograms, and the laboratory data offer a fertile field for differential diagnosis. The final roentgenogram, the absence of tubercle bacilli, and the clinical picture appear to rule out any active tuberculous infection. There was no proof of a mycotic lesion. The only organisms cultured from the sputum were non-hemolytic streptococci. This, together with the absence of a systemic reaction, the blood count, the rapidity of change in the roentgen-ray findings, and the chronicity of symptoms is against a bacterial infection. There is nothing to substantiate an amebic process. Pulmonary uncinariasis is to be considered, but the absence of hookworm parasites in the sputum and the duration of the symptoms appear to be unfavorable for such a diagnosis, although the possibility of an acute flareup during the larval migration through the bronchioles and alveoli must be considered. The examination of the serial films presents findings suggestive of an atypical pneumonia. The negative "cold agglutinin" reaction and the lack of clinical findings are against such a diagnosis.

The presence of microfilariae in the sputum can be explained on two bases: first, the patient had proved larval forms circulating in the blood stream, and it is possible that there may have been rupture of alveolar capillaries, with an outpouring of microfilariae into the alveoli; or second, the sub-mucosal lymphatics of the larger bronchioles and bronchi may have been involved in a generalized filarial infection, producing increased intraluminal tension, with resultant filarial bronchorrhoea.

The findings of an eosinophilia and microfilariae in the sputum, associated with a positive skin test in a dilution of 1:16000, suggests the possibility of an acute filarial reaction involving the bronchial lymphatics. It is further suggested that the edema and eosinophilic infiltration of these lymphatics are responsible for the transitory pulmonary infiltrations noted on roentgenograms.

O'Connor² has previously expressed the view that filarial lymphangitis is allergic in character and results when there are sufficient amounts of protein liberated from the disintegration of dying or dead worms, to overcome "the resistance set up by previous sensitization." It is believed that when large amounts of protein are liberated, the typical inflammatory manifestations of filariasis result. With minimal amounts, the reaction may result in a localized urticaria or local pain or a transient rise in temperature. Although the primary focus, harboring the disintegrating adult worm, was not found here, there is no doubt in view of the microfilariae circulating in the peripheral blood, that such a focus existed.

SUMMARY

1. A case of a South Pacific island native is presented, whose clinical history, roentgenological, and laboratory findings suggest a diagnosis of pulmonary filariasis.

2. It is believed that these findings can be explained on the basis of an acute allergic reaction, part of the constitutional and systemic nature of the disease.

3. In view of the development of the disease in American troops, it is suggested that filariasis be considered in the future, in the differential diagnosis of transitory pulmonary infiltrations.

BIBLIOGRAPHY

1. MANSON-BAHR, SIR PHILIP H.: *Manson's tropical diseases*, 1942, Cassell and Co., Ltd., London.
2. O'CONNOR, F. W., and HULSE, C. R.: Some pathological changes associated with *Wuchereria bancrofti* infection, *Trans. Roy. Soc. Trop. Med. and Hyg.*, 1932, xxiii, 444.
3. MICHAEL, P.: Filariasis among Navy and Marine personnel, report on laboratory investigations, *U. S. Naval Med. Bull.*, 1944, xliii, 1059-1079.
4. RIFKIN, H., and THOMPSON, K. J.: Observations on the structural changes occurring in filariasis, *Arch. Path.*, 1945, xl, 220-224.
5. ZUCKERMAN, S. S., and HIBBARD, J. S.: Clinico-pathological study of early filariasis, with lymph node biopsies, *U. S. Naval Med. Bull.*, 1945, xlv, 27-36.
6. WARTMAN, W. B.: Lesions of the lymphatic system in early filariasis, *Am. Jr. Trop. Med.*, 1944, xxiv, 299-313.
7. CRAIG, C. F., and FAUST, E. C.: *Clinical parasitology*, 1943, third edition, Lea and Febiger, Philadelphia.
8. STRONG, R. P.: *Stitt's Diagnosis, prevention, and treatment of tropical diseases*, Vol. II, 1943, sixth edition, Blakiston Company, Philadelphia.
9. Editorial on Filariasis: *U. S. Naval Med. Bull.*, 1945, xlv, 181.
10. KNOTT, J.: Method for making micro-filarial surveys on day blood, *Trans. Roy. Soc. Trop. Med. and Hyg.*, 1939, xxxiii, 191.
11. ZARROW, M., and RIFKIN, H.: Observations on the specificity and clinical use of *Dirofilaria immitis* antigen in the diagnosis of human filariasis (*W. bancrofti*), *Am. Jr. Med. Sci.*, 1946, ccxi, 97-102.

TROPICAL EOSINOPHILIA *

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WEINGARTEN¹ has described a syndrome called tropical eosinophilia, which is characterized by frequent early morning paroxysms of asthma, weakness, loss of weight and appetite, and a marked leukocytosis which may reach 80,000, due chiefly to a marked increase in eosinophiles which may constitute as much as 80 per cent of the total number of white cells.

Weingarten,¹ who has had the opportunity to observe 81 cases, reported that all his cases except three originated in and about Bombay, India. He stated that the disease began with lassitude, a low-grade fever rising to 100° or 101° F., with a marked loss of appetite and a corresponding loss of weight. Within a

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week the patients developed a dry, ineffective cough which was more marked at night. Then the patients began to have severe attacks of wheezing, dyspnea, coughing, and tightness in the chest, which characteristically occurred in the early morning hours and responded to the adrenergic drugs. During the febrile period the spleen was moderately enlarged, hard, and smooth, but not tender. After a period of several weeks, the patients' temperatures became normal, and there was no further loss of weight. The laboratory examinations showed a marked leukocytosis ranging from 20,000 to 80,000, with eosinophiles as high as 88 per cent of the total white cell count. All the eosinophiles were of normal size and shape and fully matured. The sedimentation rate was moderately accelerated. Roentgenograms of the chest during the febrile period showed a distinctive, disseminated mottling of both lungs. The average focus was about the size of a split pea with moderate intensity of its central shadow and ill-defined blurred outlines. Each focus had a diameter of 0.2 to 0.5 cm. The foci were more numerous and larger about the hilar region and commoner in the bases than in the apices. This mottling usually lasted for about four weeks. Roentgenograms of the chest in cases which had become *chronic* showed only prominent bronchial markings.

The cause of this disease has not been established. However, Weingarten¹ has shown that the clinical symptoms disappear and that the laboratory findings revert to normal when the patients are treated with arsenicals. He treated his cases with intravenous neoarsphenamine, giving an injection every fourth day, usually in a course of six: 0.15 gm., 0.3 gm. and 0.45 gm., repeated once or twice. The neoarsphenamine was dissolved in a 10 per cent solution of calcium gluconate, to which 200 mg. of ascorbic acid were added. After the first two or three injections, he noted a slight increase in the total leukocyte count, as well as in the percentage of eosinophiles. After five or six injections, Weingarten observed a sharp decrease in the number of white cells and the percentage of eosinophiles. Clinical symptoms disappeared rapidly after the third injection.

Emerson² described a case of tropical eosinophilia in a young man of 30 years who worked in India from 1937 to the spring of 1942. His symptoms developed in December 1942 after his return to the United States and commission in the United States Naval Reserve. He showed the usual clinical symptoms, and his white cell count rose to 32,500, with 78 per cent eosinophiles. Roentgenograms of the chest showed fine, irregular, diffuse mottling. The areas of increased density were scattered throughout both lungs, but were more marked in the hilar regions and at the bases. Emerson² treated this case with two courses of carbarsone by mouth, using 0.25 gm. twice daily for 10 days with a 10 days' rest between the two courses. He noted a slight rise in the total white cell count half way through the first course of carbarsone. However, at the end of the first course of carbarsone there was a sudden drop in the total white cell count which was accompanied by a corresponding drop in the total number of eosinophiles. Following the second course of carbarsone, the total white cell count was normal with the eosinophiles making up 9 per cent of the total white count. Soon after the end of the first course of carbarsone the asthmatic paroxysms disappeared, the roentgenogram of the chest was clear, and auscultation of the chest revealed no abnormal findings.

Chaudhuri³ saw a young male Mohammedan of 31 years of age in India with the clinical symptoms of tropical eosinophilia, a white cell count of 29,500, of

which 75.5 per cent were eosinophiles, and lungs showed by roentgenogram diffuse mottling. He was treated with intravenous mapharside injections, 0.02 gm. for the first and 0.04 gm. for four subsequent doses at five-day intervals. The clinical symptoms cleared, and the mottling of the lungs cleared after the third injection. Within four weeks the white cell count dropped to 6,200 with 16 per cent eosinophiles.

Parsons-Smith ⁴ treated a male European in Cairo, Egypt, who presented the clinical symptoms and laboratory picture of tropical eosinophilia, with neoarsphenamine as did Weingarten, and he obtained the usual restoration to health of his patient.

Robert Helig and S. K. Visveswar ⁵ treated two cases of tropical eosinophilia in India successfully with neoarsphenamine. They felt that the disease might have an allergic origin.

S. K. Vaidya ⁶ diagnosed six cases of tropical eosinophilia from 1929 to 1934. He recommended that these patients be treated with neoarsphenamine intravenously. Fellow medical men treated these cases and clinical cures were obtained. It is interesting to observe that two of these cases had frequent relapses and had to be treated with arsenicals during each relapse. Vaidya stated that tropical eosinophilia may only be cases of asthma and allied allergic conditions giving an extreme allergic response.

Menon ⁷ analyzed eight cases of tropical eosinophilia which he saw in India. He found that it was most common below the age of 30 years, and more common in males than in females. He found that the white blood cell count varied between 15,000 and 25,000. The eosinophilia was between 32 per cent and 67.5 per cent, and the sedimentation rate was increased. He suggested that this syndrome of tropical eosinophilia was due to an infection, the responsible organism being yet unidentified.

Lal ⁸ saw 15 cases of tropical eosinophilia in India. He found that arsenical medication resulted in clinical cures.

Hirst and McCann ⁹ reported a case of tropical eosinophilia in a United States Naval officer who developed symptoms while stationed in Samoa. When they saw the officer, he had had symptoms for two years. They obtained a clinical cure with intravenous neoarsphenamine as outlined by Weingarten. They failed to find the cause of this syndrome.

van der Sar and Hartz ¹⁰ saw three cases of tropical eosinophilia on Curaçao. In one case they demonstrated microfilariae in the eosinophilic abscesses and in the enlarged axillary lymph nodes. They were unable to demonstrate microfilariae in the enlarged lymph nodes of their other two cases. They viewed an autopsy in a fourth case, in which blood in the liver showed hypereosinophilia. The spleen was enlarged and the subcapsular pulp showed many eosinophiles and microfilariae. They treated their three cases successfully with arsenicals. They felt that they had demonstrated the relationship between tropical eosinophilia and filariasis. They also felt that the discussion of the treatment of filariasis with arsenic should be studied further.

In April 1944 two patients were admitted to the Cushing General Hospital with a diagnosis of bronchial asthma. Early in the morning on the day of their admission, both patients developed what appeared to be a typical paroxysm of asthma which was relieved in each case by 0.5 c.c. of epinephrine (1-1000) subcutaneously. However, they both showed elevated white blood cell counts,

15,000 in one case and 25,000 in the second patient, with a marked eosinophilia, 45 per cent in one patient and 60 per cent in the second case. I thought of Dr. Francis M. Rackemann's¹¹ statement: "All is not allergy that wheezes." In discussing the patients with Colonel John A. Isherwood, I found that a marked eosinophilia with respiratory symptoms has been seen in tropical areas. He suggested the diagnosis of tropical eosinophilia, and referred me to Emerson's² paper.

CASE REPORTS

Case 1. A 34-year-old white soldier entered the Army March 13, 1941. His past medical history revealed that the patient had had the usual symptoms of hay fever with some wheezing and dyspnea from mid-August until the first frost each year from 1923 to 1936. From 1936 he had only mild lacrimation and sneezing during his usual hay-fever season. There were no other allergic manifestations in himself or in his family. Without difficulty he completed 11 months' training as an infantry rifleman in Florida, Georgia, and Louisiana. After 21 months of service in the Southwest Pacific theater, in October 1943 he developed a severe, chronic, nonproductive cough. About two weeks later during the early hours of the morning he had severe paroxysms of wheezing, dyspnea, coughing, and tightness of his chest, which persisted for several hours. Every morning for a month his attacks continued. He lost weight and became listless. Then he was admitted to an army hospital.

There, on physical examination his chest was found to be full of sibilant and sonorous râles with occasional crackling and crepitant râles, both inspiratory and expiratory. His vital capacity averaged 2700 c.c. with no change with the use of epinephrine. During his 45 days at this hospital, his total white cell count averaged 30,000 with 75 per cent eosinophiles; repeated stool examinations were negative for ova and parasites; urine and sputum showed no ova or cysts; roentgenograms of skull and soft tissues were negative; and microscopic study of the sternal bone marrow revealed only marked hyperplasia of the eosinophilic elements of the marrow. During his stay at this hospital his weight declined from 136 to 124 pounds, and the paroxysms of coughing, wheezing, and dyspnea became more severe and appeared throughout the 24 hours, in contrast to his previous episodes, which had appeared only in the early hours of the morning.

On December 19, 1943 the patient was transferred to a Naval Hospital. He remained there for one-and-a-half months, and his clinical symptoms and laboratory picture showed no change. Then the patient was sent to a numbered General Hospital, where chest examination revealed poor expansion on inspiration, increased resonance, diminished breath sounds, moist and musical râles with wheezing throughout both lungs. A chest plate showed a slight diffuse pleural thickening and possible slight pulmonary fibrosis. The patient was evacuated from the Southwest Pacific theater on February 8, 1944, and he arrived at the Dibble General Hospital on February 22, 1944. For two months the patient's condition remained unchanged.

The patient arrived at the Cushing General Hospital on April 13, 1944. On admission he weighed 126½ pounds; blood pressure was 128 mm. Hg systolic and 80 mm. diastolic; pulse rate was 90 per minute; respirations were 22 per minute; and temperature was 98.6° F. He was found to have an asymptomatic pilonidal cyst and a deviated nasal septum. Cervical, inguinal, and submaxillary lymph nodes were palpated. The costo-phrenic angle was moderately widened, and there was some flaring of the ribs. The anterior-posterior diameter of the chest was moderately increased. Chest was hyperresonant throughout to percussion. On auscultation of lungs, breath sounds were distant and expiratory wheezes were noted in all lung fields. His vital capacity was 60 per cent of normal. In the early hours of his first morning at Cushing, the patient was awakened with a severe paroxysm of wheezing, coughing, dyspnea.

and tightness in the chest. The respiratory rate rose to 60 per minute. All lung fields were filled with both inspiratory and expiratory musical râles. The attack was relieved with 0.5 c.c. of epinephrine (1-1000) subcutaneously. He continued to have similar paroxysms of wheezing, etc., every morning, usually between the hours of one and five. The use of a saturated potassium iodide mixture and ephedrine capsules definitely lessened the severity of these episodes.

Prior to arsenical treatment, his total white cell count varied from 30,000 to 70,000, with an eosinophilia of 60 to 90 per cent. Sedimentation rate was 24 mm. per hour on admission, platelets numbered 209,000. Repeated examination of the blood for malarial parasites and microfilariæ failed to show any organisms. Repeated blood cultures were negative. Kahn, agglutination test for undulant fever, Weil-Felix test, and heterophile antibody test were normal.

A few eosinophiles, no Curschmann spirals, no tubercle bacilli, and a few epithelial cells were found in the sputum. Sputum cultures were negative for molds and fungi. An occasional erythrocyte and a few leukocytes were seen in the urine, and a catheterized specimen of urine on culture was negative. Feces repeatedly were free of parasites and ova. Repeated cultures of feces yielded only *Bacillus aerogenes*.

Microscopic examination of sternal bone marrow presented an increase in eosinophiles which were mature and normal in size and shape. Dark field and microscopic examination of a cervical lymph node and a piece of adjoining muscle was negative for organisms. The cervical lymph node contained a few normal eosinophiles. The structure of the cervical muscle was normal. Cultures of the cervical lymph node and muscle were negative.

Intradermal skin tests for Echinococci and Trichinellæ were negative. The pure protein skin test for tuberculosis was positive (4+) for the second strength.

Intracutaneous skin tests for dust, the animal epitheliums, orris root, and several of the pollens, including ragweed, timothy, and orchard grass, were positive.

Roentgenograms of the nasal sinuses showed haziness of both antra, with a marked thickening of the lining membrane on both sides. An increase of the bronchial markings of each hilar zone and in the upper portion of the right lung and a thickening of the interlobar pleura on the right was seen in stereoscopic films of the chest.

On May 23, 1944 the patient was placed on 0.25 gm. of carbarsone orally twice daily. He completed two 10-day courses of carbarsone, with a 10-day rest period between courses, on June 21, 1944. His acute paroxysms of coughing, wheezing, dyspnea, and tightness in the chest continued until July 3, 1944, at which time the attacks ceased. However, patient continued to have a few expiratory musical râles scattered throughout all lung fields. By July 27, 1944 patient was symptom-free except for some mild wheezing each morning at about five. Steadily he gained weight and energy. Then he was given the following course of neoarsphenamine intravenously: July 27, 1944, 0.15 gm.; July 31, 1944, 0.3 gm.; August 4, 1944, 0.45 gm.; and August 8, 1944, 0.45 gm. Following this course of neoarsphenamine, patient was symptom-free, and his chest was clear. He continued to gain weight and strength, weighing 145 pounds on September 11, 1944. By August 8, 1944 a roentgenogram of the chest showed only slight thickening of the interlobar pleura on the right. The intradermal skin tests for dust, feathers, ragweed, and timothy were more markedly positive in September 1944 than in April 1944. However, this could be accounted for by the fact that the patient was having some mild hay fever in September due to ragweed pollen.

Figure 1 graphically pictures his white cell count, eosinophilia, and sedimentation rate throughout the course of his illness. It is to be noted that arsenic increased the white cell count and percentage of eosinophiles at first. However, both dropped dramatically after a few days' treatment.

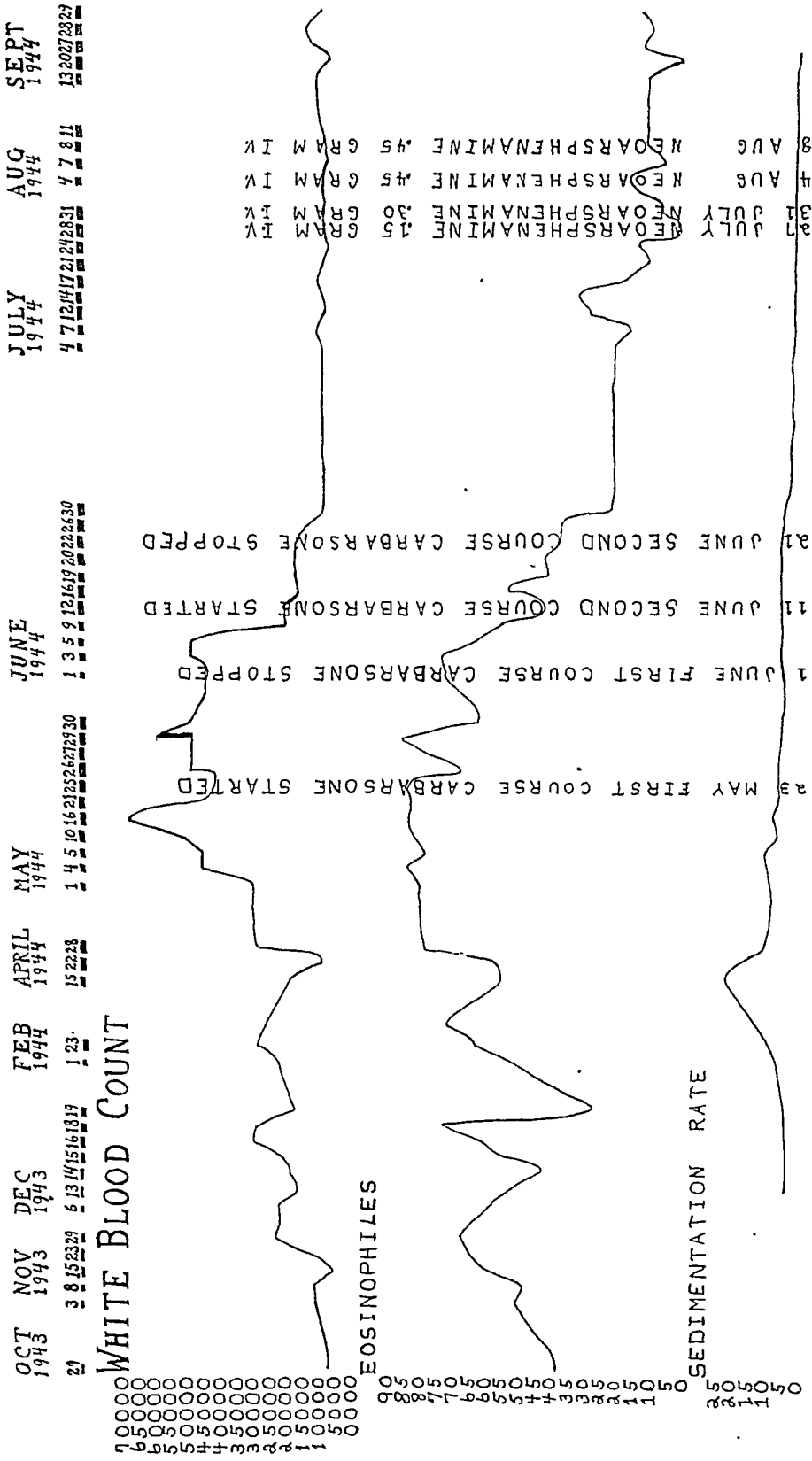


Fig. 1. Case 1.

In June 1945 the patient was seen at the Lovell General Hospital. The patient was feeling well and was working in a woolen mill. On a few occasions he had noticed some mild wheezing on getting up in the morning. However, he had not had any dyspnea. He showed nothing abnormal on physical examination. He weighed 158 pounds. His total white cell count was 8,000 with 11 per cent eosinophiles, 51 per cent neutrophiles, 35 per cent lymphocytes, and 2 per cent monocytes.

Dr. Harold W. Brown of the School of Public Health, Columbia University, supplied me with *Dirofilaria immitis* antigen for intradermal skin testing. The preparations used were prepared by Eli Lilly and Company, and include 1-1000 dilution B 7615 A, 1-10,000 dilution B 7615 A, and a control B 7615 D. The quantity of each solution injected intradermally was 0.01 c.c. A reaction was considered positive when the wheal of the antigen exceeded 3 mm. or more than that of the control wheal. The patient showed positive reaction to both dilutions at 15 minutes, at 30 minutes, at 40 minutes, and at one hour.

Case 2. A 26 year old white soldier entered the Army in October 1939. His medical history was negative for allergic diseases and their manifestations. With the exception of one sister who had mild "rose fever" in June and July of each year, the entire family was free of allergy. This "rose fever" had never been investigated medically.

Without difficulty the patient completed 26 months of infantry training in the southern section of the United States. In January 1942 he went to the islands in the Southwest Pacific theater. After 18 months in that area, in July 1943 one morning at about 4:30 a.m., patient was awakened by a severe, dry, nonproductive cough. Within the same week he began to have severe attacks of wheezing, dyspnea, coughing, and tightness in the upper anterior-posterior portion of his chest. The attacks were frequent, occurring every two to four hours and lasting 15 to 30 minutes. Gradually he lost his appetite, lost weight, and became weak. On October 30, 1943 he was admitted to an Army hospital, where he was found to have an eosinophilia of 72 per cent. He remained at this installation for two months, during which time his symptoms became more marked, particularly in the early morning hours. His weight continued to drop, and he became weaker. Repeated stool examinations showed no ova or parasites. Microscopic examination of an inguinal lymph node and sternal bone marrow showed only a marked increase in normal eosinophiles.

In December 1943, patient was transferred to a Naval Hospital. On physical examination he appeared undernourished; temperature 99.2° F.; pulse 84 per minute; and respirations 16 per minute. Throughout both lungs, most prominent at the bases and more prominent after coughing, were many sibilant and sonorous râles. Attacks of wheezing, dyspnea, and coughing appeared more frequently and severely at night. These attacks were relieved by epinephrine subcutaneously. Laboratory examinations showed: average total white cell count was 15,000, with 44 per cent eosinophiles; roentgenograms of chest showed a slight generalized fibrosis of both sides of the chest; sputum contained no acid-fast organisms, a few streptococci, and a few staphylococci; repeated stool examinations were negative for ova and parasites. He was evacuated from the Southwest Pacific theater on February 8, 1944, and arrived at the Dibble General Hospital February 22, 1944, where his symptoms and laboratory picture remained unchanged for two months.

On arrival at the Cushing General Hospital April 13, 1944, the patient weighed 108 pounds; blood pressure was 122 mm. Hg systolic and 72 mm. diastolic; radial pulse, 76 per minute; respirations, 20 per minute; temperature, 98.4° F.; and vital capacity 85 per cent of normal. Inguinal and axillary lymph nodes the size of almonds were palpated. The costophrenic angle was slightly widened, and the anteroposterior diameter of the chest was slightly increased. Chest was resonant to percussion. A few moist inspiratory râles were noted at the bases of both lungs, and a few expiratory

wheezes were found scattered throughout all lung fields. The expiratory phase of respiration was slightly increased.

In the early hours of his first morning at Cushing, the patient was awakened by a severe paroxysm of wheezing, dyspnea, coughing, and tightness in his chest. His respiratory rate rose to 35 per minute. All lung fields were filled with both inspiratory and expiratory musical râles. The attack was relieved by 0.25 c.c. of epinephrine (1-1000) subcutaneously. The patient continued to have similar paroxysms every morning between the hours of one and five. The use of a potassium iodide mixture and ephedrine capsules definitely lessened the severity of these attacks.

His total white cell count fluctuated between 20,000 and 25,000, with 50 per cent to 70 per cent eosinophiles. Sedimentation rate averaged 7 mm. per hour. Platelets numbered 221,900. Repeated examinations of the blood failed to show any malarial parasites or microfilariae. Repeated blood cultures were negative for any organisms. Kahn, agglutination test for undulant fever, Weil-Felix test, and heterophile antibody test showed no abnormalities.

Sputum examinations revealed a few eosinophiles, with no fungi, no molds, no acid-fast organisms, and no Curschmann spirals. Cultures of the sputum for molds and fungi were negative. Catheterized specimen of urine produced a few colonies of *Staphylococcus albus* on culture. Repeated stool examinations for ova and parasites were negative.

Sternal bone marrow contained an increased number of normal mature eosinophiles. Dark-field examination of an axillary lymph node and adjoining piece of muscle showed no organisms. Microscopic section of the lymph node and muscle was normal, and cultures of both revealed no organisms.

Intradermal skin tests for *Echinococcus* and *Trichinella* were negative. The pure protein derivative skin test for tuberculosis gave a positive (2+) reaction for the second strength. Patient showed positive intradermal skin tests to dust, mixed feathers, kapok, wool, orris root, and tobacco.

Roentgenograms of the paranasal sinuses were clear, and those of the chest showed an increase in density of the bronchial markings on both sides and a thickening of the interlobar pleura on the right.

On May 23, 1944, the patient started a 10-day course of 0.25 gm. of carbarsone orally twice daily. He had two courses with a 10-day rest between them, finishing the second course on June 21, 1944. Immediately following the initiation of arsenical therapy, his asthmatic-like paroxysms increased in frequency and severity. He had to be placed in an oxygen tent. He became epinephrine fast, and he was treated successfully with ether in olive oil by rectum. On May 27, 1944, his asthmatic-like paroxysms suddenly ceased. However, he continued to have expiratory musical râles throughout all lung fields and mild coughing until June 2, 1944, one day after the last day of the first course of carbarsone, at which time his coughing ceased and only a few scattered expiratory musical râles remained. He began to gain weight and regain his energy. By June 7, 1944 all lung fields were completely clear, and he had no further symptoms. On August 16, 1944, his vital capacity was 112 per cent of normal, and he weighed 118 pounds. His platelet count rose to 300,000. On August 19, 1944, intradermal skin tests showed positive reactions to dust, cow epithelium, dog epithelium, goat epithelium, rabbit epithelium, feathers, kapok, wool, orris root, and tobacco. Following arsenical therapy, his urine was normal. On September 14, 1944 a roentgenogram of his chest was normal.

Figure 2 graphically pictures his total white blood cell count, percentage of eosinophiles, and sedimentation rate in mm. per hour throughout the course of his illness. It shows that arsenical therapy increased his white cell count and percentage of eosinophiles at first. However, with a few days of therapy the white cell count and percentage of eosinophiles began to show a dramatic decrease.

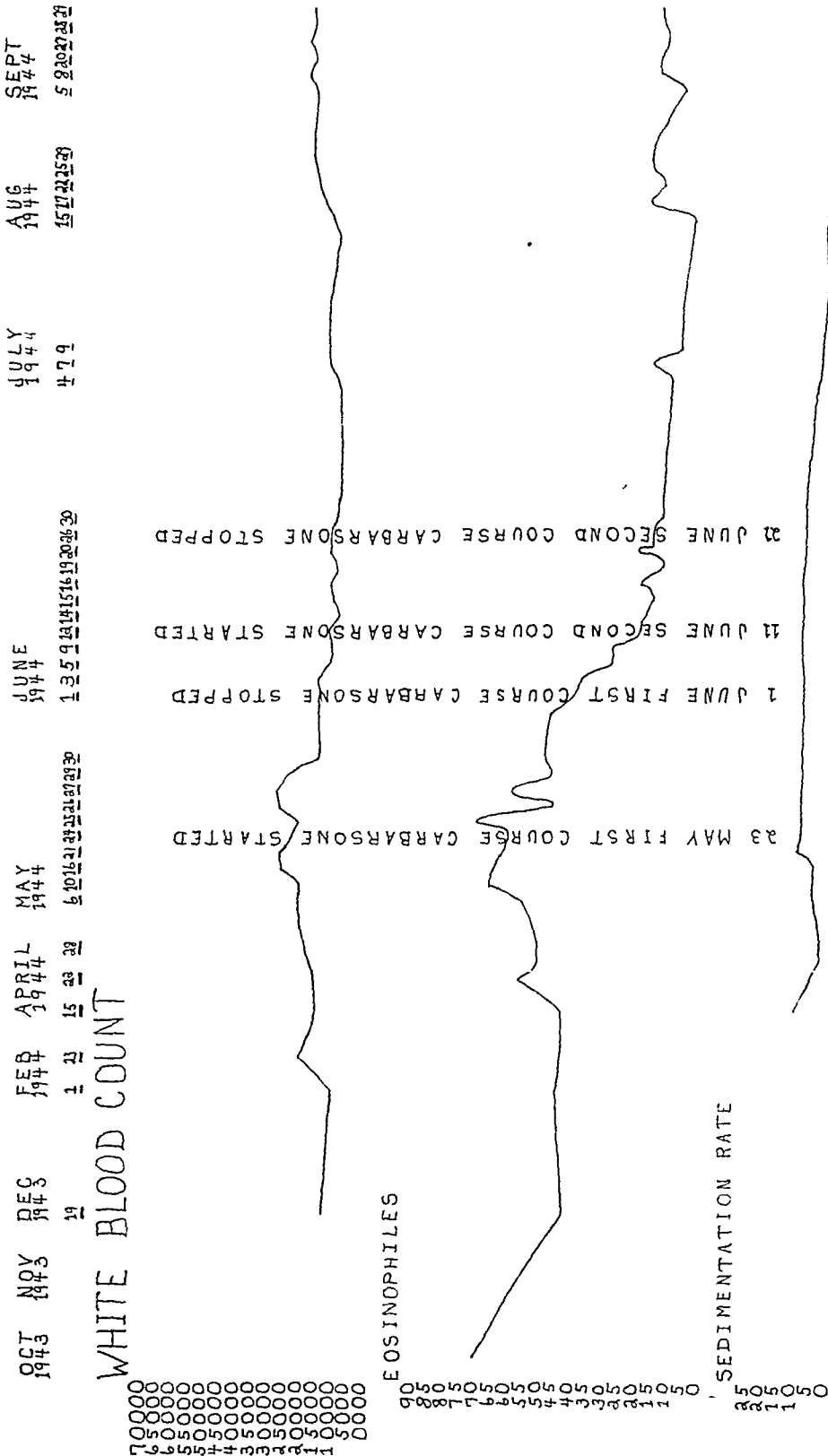


Fig. 2. Case 2.

On February 24, 1945 the patient was seen at his home. He had been feeling well, and was holding a position that required moderate physical exertion. On a few occasions on getting up in the morning he had noted some mild wheezing, which would persist for only a few moments. At no time had he experienced dyspnea, coughing, tightness in his chest. On physical examination nothing abnormal was noted. He weighed 110 pounds. His total white cell count was 13,200 with 61 per cent polymorphonuclear leukocytes, 8 per cent eosinophiles, 27 per cent lymphocytes, and 4 per cent monocytes.

In June 1945 he was seen at the Lovell General Hospital. He continued to feel well, and he weighed 115 pounds. Nothing abnormal was noted on physical examination. Intradermal skin tests were made with 1-1000 dilution and 1-10,000 dilution of *Dirofilaria immitis* and the control as prepared by Eli Lilly and Company. His tests were positive to both dilutions at the end of 15 minutes, 30 minutes, 45 minutes, and one hour. A reaction was considered positive when the diameter of the antigen wheal exceeded by 3 mm. or more that of the control wheal. His white blood cell count was 7,750, with 4 per cent eosinophiles, 61 per cent polymorphonuclear leukocytes, 33 per cent lymphocytes, and 2 per cent monocytes.

Differential Diagnosis: Colonel Johnson McGuire followed these cases with interest, and gave many helpful suggestions in establishing the diagnosis.

Since these patients spent considerable time in areas known to be heavily infested with many pathogenic parasites, various parasitic infections were considered. No parasites or ova were recovered in the blood, in the feces, in the urine, or in the sputum of either patient either at Cushing or overseas installations, although frequent and varied procedures were tried. No ova of *Schistosoma mansoni* or of *Ascaris lumbricoides*, no cysts, nor trophozoites of *Entameba histolytica* were recovered.

Ankylostomiasis was ruled out. Neither of the patients had an anemia, although they had suffered from their disease for many months. The patients did not experience palpitation, epigastric tenderness, or a tendency to mental retardation. Neither patient had chronic constipation or diarrhea. Repeated stool examinations in several medical installations revealed no hookworm ova.

All agglutination tests were negative, including Weil-Felix, heterophile antibody, and the agglutination test for undulant fever. Intradermal skin tests for *Ecchinococci* and *Trichinellae* were negative. Muscle biopsy failed to support a diagnosis of trichinosis. Attempts to culture any yeast or fungus from the sputum failed.

Loeffler's syndrome was considered. This disease is usually accompanied by a rise in temperature, cough, wheezing, and a metallic taste. Physical examination usually reveals some sibilant râles throughout the lung fields, with areas of diminished resonance. Jones and Souders¹² reported cases with a total white cell count of 10,000, with 10 per cent to 60 per cent eosinophilia. Roentgenograms show abnormal shadows that appear and disappear rapidly, only to reappear in another lung field. These roentgenographic findings are not consistent with those in the cases presented. Moreover, Loeffler's syndrome does not run as long a course as that of the cases described.

Hodgkin's disease and eosinophilic leukemia were considered. Since both patients are now quite well, it would seem fair to consider that they did not have either of these diseases.

Periarteritis nodosa could present a similar clinical and laboratory picture. However, both patients showed no tender muscles or painful nodes and had

normal blood pressure. In both cases there was an absence of peripheral neuritis. Muscle biopsy in both cases showed normal vascular tissue.

Bronchial asthma does not present a comparable laboratory picture.

Dr. Francis M. Rackemann examined both patients. He was of the opinion that neither patient had ordinary bronchial asthma or the type classified as periarteritis.

Filariasis was considered, as both patients had spent considerable time in an area where *Wuchereria bancrofti* abounds. Repeated examinations of the blood of both patients at all hours revealed no microfilariae. Examination of biopsies of enlarged lymph nodes, muscle tissue, and bone marrow failed to show any filariae. However, both patients have positive reactions to intradermal skin testing with *Dirofilaria immitis* antigen. Bozicevich and Hutter¹³ found that a 1:1,000 dilution of *Dirofilaria immitis* antigen gave false positive reactions in approximately 30 per cent of people not exposed to filariasis. They found that the number of false positives could be markedly reduced by using a 1:8,000 dilution of *Dirofilaria immitis* antigen. The patients presented had no enlargement of lymph nodes after their treatment with arsenicals.

SUMMARY

Two cases similar to those described by Weingarten¹ as tropical eosinophilia have been presented.

These cases originated in the Southwest Pacific area.

Careful clinical and laboratory study failed to establish the etiology of the disease. I feel that the possibility of tropical eosinophilia being filariasis must be kept in mind as van der Sar and Hartz¹⁰ have seen cases of tropical eosinophilia in whom they have found microfilariae. All future cases should be thoroughly searched for microfilariae.

Both cases responded to arsenical therapy. It would seem that intravenous arsenical treatment is more effective than oral therapy.

BIBLIOGRAPHY

1. WEINGARTEN, R. J.: Tropical eosinophilia, *Lancet*, 1943, i, 103-105.
2. EMERSON, KENDALL: Tropical eosinophilia, *U. S. Nav. Med. Bull.*, 1944, xlii, 118-123.
3. CHAUDHURI, R. N.: Eosinophil lung, *Indian Med. Gaz.*, 1943, lxxvii, 575-577.
4. PARSONS-SMITH, B. G.: Tropical eosinophilia, *Lancet*, 1944, i, 433-434.
5. HELIG, ROBERT and VISVESWAR, S. K.: Tropical eosinophilia, *Indian Phys.*, 1943, ii, 305-311.
6. VAIDYA, S. K.: Observations on "tropical" eosinophilia, *Indian Phys.*, 1943, ii, 358-365.
7. MENON, K. G. K.: Tropical eosinophilia, *Indian Med. Gaz.*, 1945, lxxx, 24-29.
8. LAL, A. B.: Tropical eosinophilia, *Indian Med. Gaz.*, 1945, lxxx, 30-32.
9. HIRST, W. R., and McCANN, W. J.: Tropical eosinophilia, *U. S. Nav. Med. Bull.*, 1945, xliv, 1277-1281.
10. VAN DER SAR, A., and HARTZ, H.: The syndrome, tropical eosinophilia, and microfilaria, *Am. Jr. Trop. Med.*, 1945, xxv, 83-96.
11. RACKEMANN, FRANCIS M.: New theories concerning asthma, *New England Jr. Med.*, 1944, ccxxx, 284-289.
12. JONES, S. H., and SOUDERS, C. R.: Eosinophilic infiltration of the lungs (Loeffler's syndrome), *New England Jr. Med.*, 1944, ccxxxi, 356-358.
13. BOZICEVICH, J., and HUTTER, A. M.: Intradermal and serological tests with *Dirofilaria immitis* antigen in cases of human filariasis, *Am. Jr. Trop. Med.*, 1944, xxiv, 203-208.

PENICILLIN IN THE TREATMENT OF HISTOPLASMOSIS: TWO CASE REPORTS *

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IN the past five years, histoplasmosis has been encountered with increasing frequency at the University of Michigan Hospital. In part, this may be due to a greater awareness of the disease, but this does not seem entirely to account for its increased incidence. Since December 1944, four cases of histoplasmosis have been diagnosed ante mortem at the University Hospital and variously treated. The present report is concerned with the treatment with penicillin of one of these cases, together with another case admitted to the hospital prior to 1945. None of these cases is included in the review by Parsons and Zarafonitis.¹

CASE REPORTS

R. Y., a 55 year old white male, was admitted to the hospital on June 2, 1943 complaining of perineal pain, pain on defecation, and recent chills and fever. In July 1942 he noted the onset of severe sharp shooting pains in the left inguinal region, radiating to the suprapubic region and penis. This pain persisted and was unchanged at the time of admission.

Rectal examination had revealed what was interpreted as carcinoma of the prostate, and for this he had been given 2 mg. of stilbesterol daily for four months followed by roentgen-ray castration.

In September 1942 a roentgen-ray diagnosis of gastric ulcer was made, and in January 1943 a partial gastric resection was done. The pathological diagnosis was subacute purulent gastritis. Foreign-body giant cells and large collections of eosinophiles were present.

Two weeks prior to admission to the University Hospital the patient developed diarrhea, chills, fever, and severe dysuria.

After admission two cystoscopic examinations revealed chronic active trigonitis with lesions of cystitis cystica in various stages of development. This was believed to be secondary to an extra-vesical inflammatory process. Biopsies revealed polypoid fragments of bladder mucosa showing active chronic inflammation. Sigmoidoscopy demonstrated an extra-rectal mass which was extremely tender and about 6 cm. above the anus. Biopsy revealed atrophic catarrhal proctitis. Beneath the mucosa there was a single granulomatous focus with necrotic material in the center. Colon roentgenograms were interpreted as showing a narrowing and irregularity probably due to an extrarectal mass. Para-rectal surgical exploration yielded no evidence of an inflammatory or neoplastic mass of any kind. Chest roentgenogram on June 4, 1943 was negative. The hemoglobin was 13.1 gm. and the sedimentation rate was elevated. The white blood cell count was normal. Urinalysis showed a few white blood cells and mixed organisms. Blood serologic reaction was negative. He was discharged on June 6, 1943 with the diagnoses of chronic trigonitis with cystitis cystica and questionable old seminal vesiculitis.

He was readmitted to the hospital on Dec. 8, 1944 because of weakness and fever. He stated that subsequent to his discharge in June 1943, his weakness, ease of fatigue, and rectal pain gradually subsided over a six month period. He had no further rectal or inguinal pain and had returned to strenuous work. In August 1944 he developed

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From the University Hospital, Ann Arbor, Michigan.

severe bilateral temporal headache, chills, fever, and night sweats. His fever persisted and in November 1944 he became bedfast because of weakness and daily chills and fever. His temperature did not exceed 104.5° F. For the two weeks prior to admission he had a severe cough productive of one-half cup of thick sputum. The sputum varied from rusty to yellowish-green in color and was foul to the taste. Dyspnea and orthopnea were present. There had been considerable weight loss. During the last two weeks before his admission to the hospital he had been given one gram of some sulfonamide every four hours.

Physical examination at the time of admission revealed the following significant findings: he was acutely ill and orthopneic; the nasal mucous membrane was mildly injected and there was a small amount of exudate on the right tonsil; there was generalized lymphadenopathy of slight degree without any associated tenderness, fixation or matting of the nodes; there was evidence of consolidation in the right mid-lung field; there was tenderness in the region of the gastrectomy scar; the testes were atrophic; rectal examination revealed the same extra-rectal mass previously noted. Roentgen-rays revealed extensive consolidation in the base of the right upper lobe, non-visualization of the gall-bladder, and profound deformity of the upper one-half of the stomach, nature indeterminate. Urinalysis was negative. Hemoglobin was 13.8 gm. The total red blood cell count, total white blood cell count and differential count were normal. The sputum was negative for acid-fast bacilli on concentrate and culture.

Throughout this admission his temperature was septic in type, varying from 93.4° F. to 105° F. Penicillin in dosage of 20,000 units every three hours was administered intramuscularly from Dec. 13, 1944 through Dec. 23, 1944. Bronchoscopy on Dec. 22, 1944 was negative. He went into shock on Dec. 24, 1944 and died seven hours later. Penicillin had no effect on the fever or the clinical appearance of the patient. He received a total of 1,580,000 units of penicillin.

At autopsy, histoplasmosis was found involving the right lung, spleen, liver, kidney, and bone marrow. There was a severe chronic peri-esophagitis with partial obstruction of the lower esophagus. After autopsy the biopsy taken at sigmoidoscopy on June 7, 1943 was reviewed and a few *Histoplasma* were found in the submucosal granulomatous focus. Figure 1 shows the organisms in a section.

F. F., a 30 year old white female, was first admitted to the University Hospital on Sept. 11, 1944 complaining of a painful right hip of one month's duration. In July 1943 she suddenly developed a soft, tender, red, hot swelling in her right lower quadrant. There were no constitutional manifestations. About five days later an appendectomy was performed. Three months pregnant at the time, on the third post-operative day she aborted. This was followed by puerperal sepsis and she was severely ill for several months. She was given sulfonamides during this period. Recovery was apparently complete and she returned to work as an electroplater. In October 1943 she developed a dry non-productive cough which persisted until February 1944. In November 1943 she noted a gradually progressive swelling in the right cervical region which enlarged to the size of a hen's egg. This was hot, painful, tender, and reddish-purple in color. It was accompanied by afternoon fever as high as 102° F. and occasional night sweats. Daily fever persisted from this date until admission to the University Hospital in September 1944. The mass in the neck was incised and drained a yellowish watery fluid for eight months before healing. In January 1944, splenomegaly and hepatomegaly were noted for the first time. In the same month a gradually enlarging swelling was noted on the right wrist. This manifested the same characteristics as the previous swelling in the neck. Jaundice was present throughout April 1944 and her liver was exquisitely tender. The tumor on the right wrist was incised in May 1944 and discharged a sanguino-purulent fluid. Healing was delayed. During May she was given 1,000,000 units of penicillin intramuscularly in divided doses at two hour intervals. Chest roentgenograms at the local

hospital revealed slight prominence of the right hilar shadows. Two weeks after the course of penicillin was completed, tumefactions appeared on her forehead, two on her right leg, and two on her left leg. These all drained and superficially healed with the exception of the two on the right leg which were still draining at the time of admission to University Hospital. On September 1, 1944, she again developed a mild cough which was productive of small amounts of yellowish sputum. Weight loss was gradual, amounting to 44 pounds. Her past history was not contributory to the present illness. She had worked as a housewife and electroplater; she had also been engaged in the manufacture of mat landing strips for airplanes.

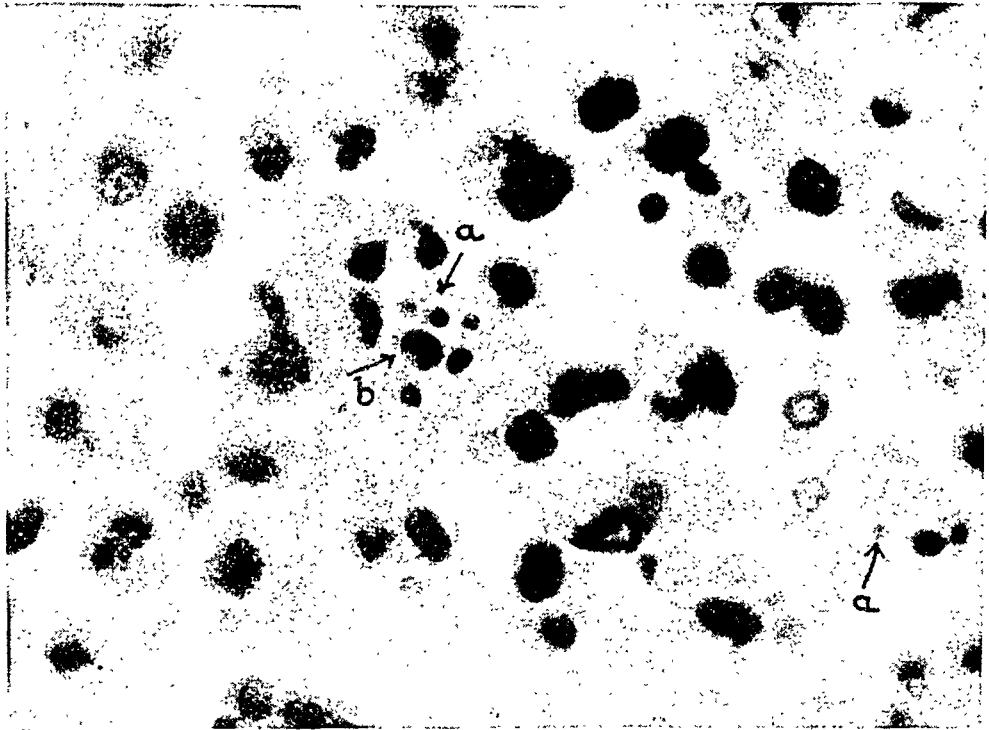


FIG. 1. Alveolar phagocytes in pulmonary exudate showing (a) *Histoplasma* of usual size ($2-4\mu$), and (b) less common large yeast form of *Histoplasma* ($6-7\mu$). Hematoxylin and eosin. $\times 1350$.

Physical examination at the time of admission revealed her to be emaciated and pale. The temperature was 100°F. , and the blood pressure was 95 mm. Hg systolic and 60 mm. diastolic. There were two draining granulomatous lesions on the right calf, one on the left calf and one on the left thigh. Healed lesions were seen on the wrist and the right side of the neck. There was a tender fluctuant nodular lesion on the forehead with a brownish-purple discoloration. The healed lesions were roughly linear with a hypertrophic pigmented type of scar. There was no generalized lymphadenopathy. The spleen was palpable. The liver was palpated 3 cm. below the right costal margin in the midclavicular line and was slightly tender. There was pronounced tenderness over the right hip with associated muscle spasm. Chest roentgenograms revealed right hilar adenopathy and patchy pneumonitis of the right lung, which gradually regressed during the next two months without entirely disappearing. Roentgenograms of the pelvis, lower extremities, esophagus, stomach, and small bowel were negative.

The total red blood cell count was 3,900,000. The hemoglobin was 10.9 gm. The total white blood cell count was 4,850. Differential count was essentially normal. Sternal and splenic aspiration revealed no Histoplasma. Twenty-five ml. of venous blood were centrifuged on Oct. 13, 1944 and again on Feb. 24, 1945. No Histoplasma were found in films made from the buffy coat. Urinalysis was negative. Brom-sulfalein liver function test showed 40 per cent retention at 30 minutes. The Mantoux test with 1:10,000 O.T. was positive. Intracutaneous histoplasmin gave a 3 by 2 cm. induration in 48 hours and a 5 by 3 cm. area in 72 hours. Broth control was negative. The blood serologic reaction was negative. Sputum culture for fungi on Sept. 15, 1944 revealed only a slight growth of monilia. Cultures taken from a skin ulcer were negative for fungi. Blood cultures taken on Oct. 5, 1944 and Nov. 9, 1944 were negative for Histoplasma, aerobes, and anaerobes. Stool culture for the typhoid-paratyphoid-dysentery group and Histoplasma was negative on Nov. 14, 1944.

Biopsy from a leg ulcer on Sept. 13, 1944 was reported as showing a "chronic infective granuloma which cannot be diagnosed on histological characteristics alone. No organisms are found on routine preparation." A biopsy from the forehead lesion on Sept. 19, 1944 was reported as: "This is a chronic infective granuloma. It does not have the characteristics of blastomycosis since it produces epithelioid tissue around caseous centers. Staining for tubercle bacilli on the previous specimen from this patient has given only negative results. If syphilis has been excluded by history and serological test, histoplasmosis seems to us to be the most probable diagnosis, but as yet we have failed to demonstrate any organisms." A biopsy taken from an ulcer of the left thigh on Sept. 29, 1944 was reported similar to the biopsy from the forehead.

Throughout this period of hospitalization she ran a low grade fever with occasional peaks to as high as 103.8° F.

She was given ultra-violet light to the skin lesions on four occasions with noticeable improvement. She gained 14 pounds in weight and was discharged on Nov. 22, 1944.

She was seen for check-up examination in the medical clinic on Jan. 22, 1945. At that time she stated that she was feeling quite well, although low-grade fever had continued. She had remained at strict bed rest. The skin lesions appeared to be quite well healed, leaving deep purplish indurated scars. The liver and spleen were still enlarged. Chest roentgenogram on this date revealed linear areas of increased density in the right lower lung, principally in the right middle lobe, showing increase in discreteness since November 1944.

Shortly after returning home from the clinic visit of Jan. 22, 1945 she became much worse. Her temperature at times rose as high as 104° F. and her cough became more severe. For several weeks she raised small amounts of yellowish sputum daily. Chest pain was present with dyspnea for the two weeks prior to her second admission on Feb. 24, 1945. For several weeks she had had periods of nocturnal delirium.

On her second admission the anterior cervical lymph nodes were moderately enlarged. Mild clubbing of the fingers was noted. During her second hospitalization her temperature varied from 96° F. to 104.6° F. taken rectally. She was irrational and comatose most of the time, although at times she was perfectly lucid. Chest roentgenogram on Feb. 24, 1945 revealed widely disseminated parenchymal disease in both lungs developing for the most part in the past month. Direct examination of the sputum on Feb. 25, 1945 revealed a rare intra-cellular *Histoplasma capsulatum*. The sputum was also positive for type 6 Pneumococci and *Hemophilus influenzae*. A small sputum sample was specially treated and injected into guinea pigs. This is discussed together with the bacteriological studies made at autopsy.

It was planned to treat her with stilbamidine but, since she had received penicillin in May, it was decided to note the effects of large doses of penicillin. She was given 20,000 units of penicillin intramuscularly every hour from Feb. 27, 1945 until her

death on March 3, 1945. She was also given 20 ml. of adrenal cortical extract on three of these days. No perceptible effect of penicillin in this dosage was noted other than a regression in the size of the liver and spleen, which could not be attributed definitely to penicillin. She received a total of 1,800,000 units of penicillin during this admission.

At autopsy the essential pathological diagnoses were: "Histoplasmosis. Mixed infection with tuberculosis (both *Histoplasma capsulatum* and tubercle bacilli demonstrated). Bilateral confluent necrotizing pneumonitis. Extensive granulomatous peritonitis with multiple adhesions, tubercle-like lesions, and abscesses. Extensive liquefy-

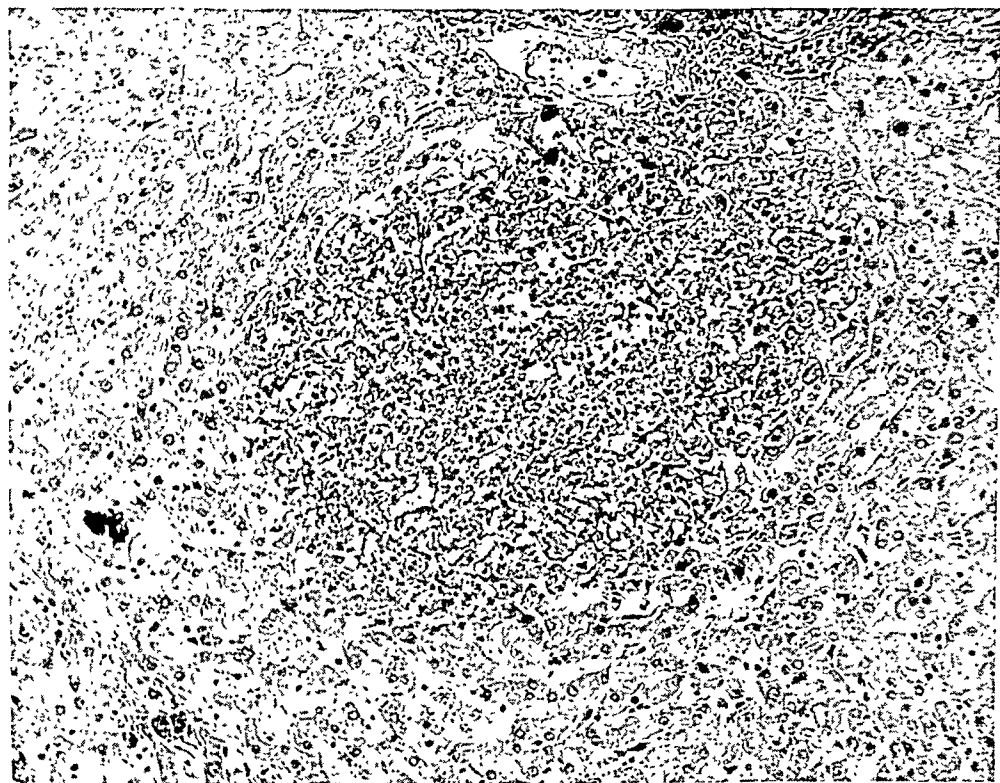


FIG. 2. Granulomatous focus of histoplasmosis in liver. Note the practical absence of tissue reaction to the area of necrosis. Histoplasma are present at the periphery of the granuloma. Hematoxylin and eosin. $\times 150$.

ing lesions in liver and abdominal lymph nodes. Miliary lesions in brain, spleen, liver, thyroid, capsule of the pituitary body, adrenals, kidneys, and urinary bladder. Chronic granulomatous salpingitis. Chronic adhesive pleuritis. Old fibrocalcareous tuberculosis of the right upper pulmonary lobe. Healed and healing lesions of the skin." The appendix was surgically absent. One area in the large intestine showed a tiny ulceration communicating with a subserosal structure containing much thick, creamy exudate. A single inflammatory lesion in brain sections had a necrotic center in which there were small bodies indistinguishable from *Histoplasma* in routine stains. In the lungs *Histoplasma capsulatum* was present in enormous numbers in granulomatous foci. The interior of a venous thrombus was nearly filled with *Histoplasma*. Very large numbers of this organism were found in the spleen. In the large intestine there were encapsulating caseous foci on and beneath the serosa, some of which were very

rich in *Histoplasma*. In the bone marrow there were occasional small foci of necrosis which resembled primary tuberculous necrotic foci, but *Histoplasma* were found in these lesions. In the oviducts a chronic granulomatous salpingitis and peri-salpingitis were present. *Histoplasma capsulatum* was present, but the pathologist believed that this probably represented a mixed infection. Tubercle bacilli were demonstrated in some of the miliary granulomatous foci in the liver. Figure 2 shows a granuloma of the liver due to histoplasmosis.

Numerous cultures were made from various tissues at autopsy. Some of these were positive for *Histoplasma capsulatum* and *Mycobacterium tuberculosis*. Of especial interest are the antemortem sputum sample and several bits of postmortem tissue. Both the sputum sample and the ground autopsy tissue were treated with penicillin in an amount to make the total concentration in each case four units per ml. These materials were then inoculated into guinea pigs. The guinea pigs were autopsied and revealed infection with *Histoplasma capsulatum*. The guinea pig inoculated with ground postmortem tissue also exhibited tuberculosis.

DISCUSSION

Neither of the two cases reported received penicillin in very large total dosage nor was it administered for a considerable length of time. It is true that the second patient received 480,000 units per day, but only for four days. It may, of course, be argued that the relatively large doses of penicillin administered during the second course of treatment in the latter case carry no greater weight in regard to the value of penicillin in histoplasmosis than does the small dosage employed in the first case. This would be true if an effective dose level were attained by the dosage used in the first case inasmuch as there is probably no real advantage in exceeding the level of effective dosage. However, at the time of treatment of both cases no data were at hand to suggest what the minimum effective level might be. It was hoped that 20,000 units of penicillin every hour would attain an effective level, if such is practicably attainable with penicillin. There is no question but that the duration of this dose level, whether effective or not, was altogether too short.

It is obvious from the pathology of histoplasmosis that no great amelioration of the disease can be anticipated in a period of a few days. However, one would expect an initial rapid decrease in the number of organisms to occur if the organism is susceptible to the concentration of penicillin present. The ready growth of *Histoplasma* from autopsy material and the abundance of normal appearing organisms in this material suggest that an effective level was not reached or that the organism was entirely insensitive to penicillin. Penicillin, in the concentration of four units per ml., was ineffectual in preventing the growth of *Histoplasma* when inoculated into guinea pigs. There is no assurance that a significant level of penicillin was maintained for an adequate length of time after this material was injected. It may be significant that the animals so inoculated were protected from the type 6 Pneumococci and the *Hemophilus influenzae* which had killed other guinea pigs and mice in less than 24 hours.

In vitro susceptibility studies with *Histoplasma* suggest that this organism is not inhibited by a concentration of 10 units of penicillin per ml. of broth. Susceptibility studies with other chemotherapeutic agents are in progress, but this work is not yet completed.

CONCLUSIONS

Two cases of histoplasmosis treated with penicillin over a brief interval of time showed no response to this treatment.

Bacteriological studies, at present incomplete, suggest that *Histoplasma capsulatum* is not susceptible to penicillin in concentrations clinically attainable.

BIBLIOGRAPHY

1. PARSONS, R. J., and ZARAFONETIS, C. J. D.: Histoplasmosis in man: Reports of seven cases and a review of 71 cases, Arch. Int. Med., 1945, lxxv, 1-23.

DEATH DUE TO ADMINISTRATION OF TYPHUS VACCINE *

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A recent editorial note in The United States Army Medical Bulletin states that a number of severe reactions due to typhus vaccine have been reported to the Surgeon General's Office, but that the number is negligible in comparison to the number of doses of egg vaccine administered. We have had occasion to observe all autopsied material in a South Pacific base. Only one case has come to autopsy as a result of typhus vaccine administration. Roth² has recently reviewed 32 cases of reactions to typhus vaccine. These reactions have been divided into two types. The first group consists chiefly of a constitutional reaction which is explained on the basis of foreign protein sensitivity. The second group is considered to be an allergic reaction to some constituent, possibly residual egg protein. The question of antigenicity of egg yolk is considered. One authority³ mentions that sensitization to egg yolk has been reported but its actual existence is doubtful. Recent unpublished observations⁴ made in the Division of Virus and Rickettsial Diseases, Army Medical Center, have revealed that egg yolk is antigenic and that sensitization to egg yolk does occur. We have recently had occasion to autopsy a young soldier who apparently was egg sensitive and had been given 1 c.c. of typhus vaccine as a prophylactic measure.

CASE REPORT

A 24 year old white male soldier had been given 1.0 c.c. of typhus vaccine subcutaneously. Eight minutes following the administration of vaccine, he complained of severe difficulty in breathing. His respirations became shallow and irregular. There developed an extensive cyanosis of his entire body. Pulse was 140 per minute; blood pressure was lowered to 80 mm. Hg systolic and 40 mm. diastolic. Five minutes following this acute onset, the patient went into sudden and deep coma. Irregular spasmodic and convulsive movements of the lower extremities developed. Twelve minutes later all respirations and pulse had ceased, despite artificial respiration and administration of epinephrine. The patient's previous immunization record is noted in table 1.

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† At present with the Dept. of Medicine, Montefiore Hospital, Gun Hill Road, New York City.

TABLE I

Vaccine	Dose	Method	Date	Reaction
Smallpox		Scratch	12/ 9/42	Immune reaction
Typhoid:				
1st Injection	0.5 c.c.	Subcutaneous	12/16/42	Headache, malaise, slight generalized pruritus, developing 20 minutes following injection and persisting for six hours
2d Injection	1.0 c.c.	Subcutaneous	12/23/42	
3d Injection	1.0 c.c.	Subcutaneous	12/30/42	
Typhoid (Stimulating injection)	0.5 c.c.	Subcutaneous	12/20/43	Slight malaise
Tetanus:				
1st Injection	1.0 c.c.	Subcutaneous	1/23/43	Slight malaise and headache, persisting for four hours following injection
2d Injection	1.0 c.c.	Subcutaneous	2/14/43	
3d Injection	1.0 c.c.	Subcutaneous	3/ 7/43	
Typhus	1.0 c.c.	Subcutaneous	10/20/44	Symptoms and signs of anaphylactic shock with resultant death

This revealed no previous administration of typhus vaccine. A review of the patient's past medical history revealed no severe illnesses. He had been on prophylactic atabrine 0.7 gm. per week for one year. He had never been hospitalized for malaria. A note is made in the out-patient record that "The patient gives a history of nausea, vomiting, and lassitude, invariably following ingestion of eggs, both raw and cooked. Almost constantly, smells such as cake and pie are followed by a feeling of fullness and nausea." No attempt, however, had apparently been made prior to typhus vaccine administration, to confirm a diagnosis of egg sensitivity by intradermal injection of diluted vaccine.

Necropsy

Gross Findings: Autopsy was performed two hours following death. The body was that of a well-developed, well-nourished young white male, weighing 165 pounds and measuring 169 cm. in length. A distinct yellow-brown pigmentation of the skin was noted over the entire body. The sclera of both eyes revealed a similar yellow-brown pigmentation. The pleural and peritoneal cavities revealed 8 c.c. and 20 c.c. of yellow-amber fluid respectively; 5 c.c. of light yellow fluid were noted in the pericardial cavity. Numerous petechial hemorrhages were noted on the posterior surface of the base of the left ventricle. These were superficially located, circular in outline, and measured 3 to 5 mm. in diameter. There was diffuse dilatation of the right auricle and ventricle, denoted by flattening and increased interspaces between the trabeculae carneae and pectinate muscles. The wall of the right and left ventricles measured 4 mm. and 7.5 mm., respectively. The right and left lungs weighed 950 and 850 gm., respectively. Each lung revealed such extensive emphysematous-like inflation that they completely filled their respective pleural cavities. Distinct subpleural blebs were noted in the right and left upper lobes. Tiny petechial hemorrhages measuring 3 to 5 mm. in diameter were noted throughout all lobes. The lung parenchyma was gray-blue, crepitant, elastic, and feathery in consistency. On section, no areas of consolidation were noted. The lumina of the bronchi and bronchioles were not dilated. A thin serous fluid was noted within the lumen of the small bronchi in the region of the right and left lower lobes. The mucous membrane was smooth, pink-red in color, and free of hemorrhage, ulceration or an endo-bronchial lesion. The

vessels revealed no thrombi or emboli. The lymph nodes were not enlarged. Except for moderate congestion of the liver, spleen, kidney, and pancreas, no other remarkable features were noted.

Microscopic Findings: The most prominent findings were noted throughout all sections of the right and left lung. The alveoli were enlarged four to five times their usual size. The alveolar walls were stretched so that they appeared as thin, irregular, wavy hair lines (figure 1). Communication between alveoli existed as a result of rup-



FIG. 1. Section through left upper lobe. Note the intense emphysema throughout. Hematoxylin and eosin. $\times 500$.

ture of alveolar septa. No exudate was present within the alveoli. The capillaries were congested. In a number of focal areas, diapedesis of red blood cells into the inter-lobular septa was seen. Clumps of mononuclear histiocytes, containing fine, brown amorphous granular pigment were present with the large alveoli. Lining the small bronchi and bronchioles was a hyperplastic and stratified columnar epithelium. This epithelium projected into the lumen in an irregular fashion, so that it assumed a distinct scalloped appearance. The lumen itself was not dilated. It contained a thin pink-staining exudate which was infiltrated by small aggregates of round cells and eosinophilic leukocytes (figure 2). A similar eosinophilic infiltration was noted throughout the mucosa and submucosa producing moderate thickening of the small bronchial and bronchiolar walls (figure 3). The mucosal vessels were moderately congested. No fragmentation and splitting of the elastic fibers were noted. The muscle fibers and cartilage plates were intact. Sections from the abdominal viscera revealed a moderate congestion throughout. No other remarkable features were noted. Microscopic examination of multiple sections of the brain was normal.

COMMENT

Death here appears to have been essentially due to anaphylactic shock secondary to typhus vaccine injection. The patient had apparently been known to be egg sensitive. It is suggested, therefore, that this reaction was allergic in nature, and the antigenic substance appears to have been egg protein, possibly albumin or egg yolk. It is of interest to theorize whether death could have been avoided if confirmation of egg sensitivity had been made by intradermal injection of diluted vaccine.

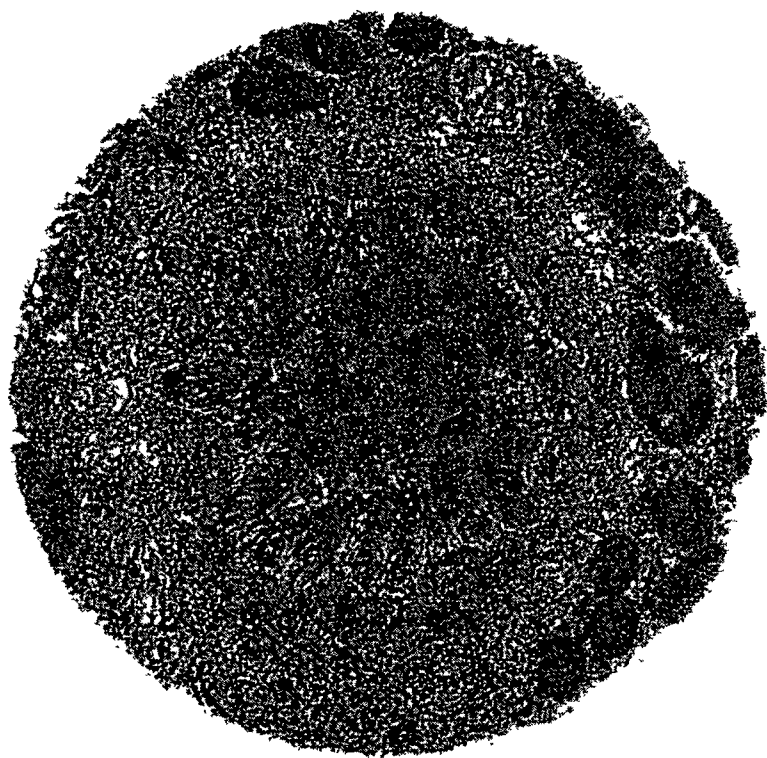


FIG. 2. Section through small bronchus, right upper lobe. Note the scalloping of the epithelial lining, the eosin staining luminal exudate with eosinophilic infiltration, and the thickening of the bronchial wall by eosinophilic and round cell infiltration. Hematoxylin and eosin. $\times 350$.

The predominating findings are noted in the respiratory system. These consisted chiefly of a severe bilateral and diffuse emphysema, a striking eosinophilia in a thin eosin-staining luminal exudate, and eosinophilic infiltration of the walls of the small bronchi and bronchioles. The morphologic findings suggest the bronchial passages as the shock organ. A comparison with acute anaphylactic shock in guinea pigs is immediately drawn. It may well be that the pulmonary findings were the result of tetanic contraction of the bronchial musculature with eventual asphyxia.

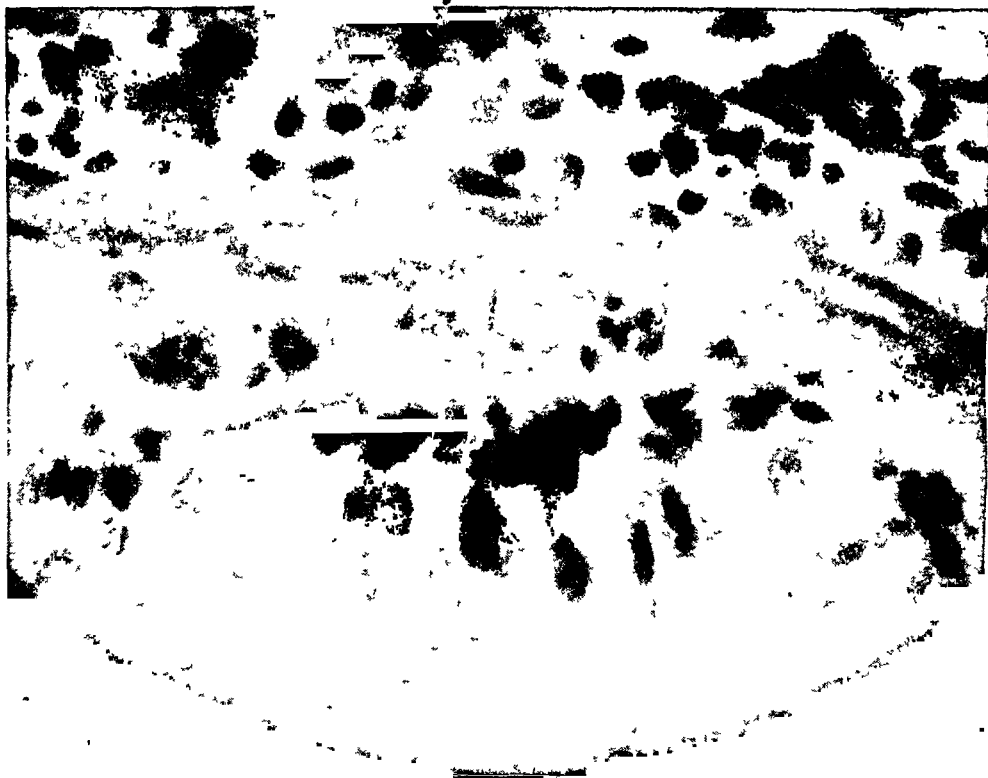


FIG. 3. Section through wall of small bronchus, right upper lobe. Note the hyperplastic columnar epithelium, and cellular infiltration of the mucosa. Hematoxylin and eosin $\times 650$.

CONCLUSIONS

1. A case is reported of an egg-sensitive soldier in whom a typhus vaccine reaction developed, with eventual death.
2. It is believed that the shock organ here was the respiratory passages, and that the anatomical findings are consistent with those noted in acute anaphylactic shock in guinea pigs.
3. It is suggested that all patients who are to receive typhus or other egg-yolk vaccine, who are suspected of being egg sensitive, be given an intradermal injection of diluted vaccine to confirm such a suspicion

BIBLIOGRAPHY

1. Editorial Note. U. S. Army Med. Bull., May 1945, No. 88, p. 111
2. ROTH, V. E.: Reactions to typhus vaccine, U. S. Army Med. Bull., 1945, No. 88, pp. 111-113.
3. TUFT, L.: Clinical allergy, 1937, W. B. Saunders Co., Philadelphia.
4. Editorial Note: U. S. Army Med. Bull., 1945, No. 88, p. 112

REGIONAL ILEITIS INVOLVING THE ILEUM, CECUM, ASCENDING COLON, AND TRANSVERSE COLON *

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SINCE 1932 when Crohn, Ginzburg, and Oppenheimer¹ first published their paper on 13 cases showing necrotizing cicatricial inflammation of the terminal ileum, many reports have appeared in the literature on the subject of granulomatous ileocolitis, commonly called "regional ileitis." Reports of cases showing widespread involvement of the cecum, ascending and transverse colon, as well as of the terminal ileum are uncommon. Bockus and his associates report 21 cases of regional ileocolitis,² seven of which showed involvement of terminal ileum and colon proximal to the sigmoid. Ravdin and Johnston³ in a summary of the literature tabulate 10 instances in a series of 393 cases in which the disease process is entirely confined to the cecum.

The disease was originally believed to involve principally the terminal ileum in a chronic, granulomatous process and was characterized clinically by the presence of anemia, diarrhea, abdominal pain, low grade fever, and a mass in the right lower quadrant. Later it was observed that other segments of bowel could be involved by a similar process, particularly the upper part of the ileum, the lower jejunum and the proximal portion of the colon. In many cases, areas of pathologic involvement alternated with normal bowel for a variable distance. Some authors have attempted to distinguish between "regional ileitis" and "regional colitis" as separate entities, but the pathologic changes are so specifically similar that the disease is undoubtedly one and the same irrespective of the part of the intestine attacked. The case reported here illustrates this fact particularly well since the major portion of the disease involved the cecum, ascending colon, and transverse colon, and extended in lesser degree to the terminal ileum and the distal portion of the transverse colon.

Many authors believe that the disease should be called granulomatous ileocolitis because of the characteristic granulomatous lesion in the wall of the intestine, which has often been described and which presents a distinctive pathologic picture. Its marked histologic resemblance to tuberculosis has often been noted; however, cultures, smears, and guinea pig inoculations of stool specimens and of operative specimens have consistently failed to reveal any evidence of tubercle bacilli.

No definite etiological factors have been determined, although acute bacillary dysentery has been suspected of having some etiological relationship. Following the epidemic of acute bacillary dysentery in Jersey City, Felsen⁴ reported 29 cases of acute inflammation of the distal ileum as an early complication, and observed at operation that the ileum was red, edematous and thickened. Bacteriologic examinations were negative for organisms of the dysentery group, although many cases had a history suggestive of a previous bacillary dysentery. Some cases, as well as the case reported here, have shown positive serum agglutination tests for the dysentery organisms in high dilutions. It may be conjectured from

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Felsen's observations that the bacillus dysentery is the primary causative agent in some cases of regional ileocolitis. Chronic, ulcerative colitis has also been suspected of having some relationship to regional ileocolitis, although the pathological picture is not at all similar. Crohn believes that chronic ulcerative colitis and chronic regional ileitis may represent different residual phases of earlier dysentery infection, but this belief lacks clinical, bacteriologic, or pathologic evidence.

The clinical diagnosis of granulomatous ileocolitis is based primarily on roentgenological findings. These vary according to the stage in which the disease is discovered. In the very early stage nothing more than irritability, localized spasm and hypermotility of the involved segment (usually the terminal ileum) may be seen. As the disease progresses, this portion of the intestine becomes smooth, thickened and contracted, with narrowing of the lumen producing the typical "string sign." There is obliteration of the normal mucosal pattern and on spot pressure film ulceration of the mucosa of the involved segment may be demonstrated. The margins of the diseased portion are slightly fuzzy and irregular as a result of ulceration. In the later stages it is not uncommon to have marked constriction sufficient to cause obstruction associated with dilatation of the intestine proximal to the lesion, accompanied by the development of fistula. Roentgenologically, the extent of involvement is often sharply demarcated. It is the experience of many roentgenologists that a barium meal will demonstrate findings of greater value in this disease than will the barium enema. However, no case should be subjected to operation without a barium enema. Examination of postoperative or autopsy specimens, however, usually reveals macroscopic and microscopic evidence of diseased bowel extending beyond the point of demarcation.

From the roentgenologic standpoint, the differential diagnosis usually limits itself to regional ileitis and ileocecal tuberculosis. Primary enterocolic tuberculosis is relatively rare. In the absence of pulmonary tuberculosis and with the inability to recover acid fast organisms from the stool, intestinal tuberculosis can usually be excluded, although an occasional case cannot be distinguished from regional ileitis, except at operation. Neoplasm, appendiceal abscess and Meckel's diverticulitis should be considered, but the history and the roentgen-ray findings are usually sufficient to exclude these.

Clinically, the early symptoms of regional ileitis closely resemble those of acute appendicitis. This is illustrated by the fact that at least 50 per cent of the reported cases of regional ileitis have a history of a previous appendectomy. In the later stages of the disease, however, the resemblance to appendicitis is less striking. Amebic colitis, chronic bacillary dysentery and ulcerative colitis must be considered in the differential diagnosis. Amebic colitis usually will show typical small discrete punched-out ulcers in the lower bowel with pus and blood in the stool, and the amebae may often be recovered from a warm stool specimen. Ulcerative colitis can usually be diagnosed by roentgen-ray and the sigmoidoscopic examination. The diagnosis of chronic bacillary dysentery depends on the isolation of the specific organism from the stool, and rising serial serum agglutination titers.

It is the general consensus of opinion that the only satisfactory treatment of granulomatous ileocolitis at the present time is surgical, although recently there is a growing feeling that some cases, especially those showing minimal involve-

ment, may respond to medical treatment. Maintenance of an optimum nutritional status with periodic exposures to ultraviolet ray are helpful. As Marshall⁵ points out, there is considerable difference of opinion as to the time and type of operation that may be indicated. There is general agreement that all of the diseased bowel and the diseased mesenteric glands must be removed if a satisfactory result is to be obtained. In this connection, it is important for the surgeon to remember that more than one portion of the bowel may be involved, so that in all cases a complete exploration of the intestinal tract from the duodenum to the rectum should be done. The type of operation which is advised is a wide resection of the affected bowel with its mesentery with a primary end to end or side to side anastomosis. Marshall prefers the two stage Mikulicz type of operation, particularly in the presence of secondary infection. When there is a secondary abscess present, it may be necessary to drain the abscess first and to carry out the necessary resection at a later date. The immediate results of this procedure have been very variable. Even in the best hands, there has been at least a 10 per cent recurrence after complete resection of the diseased bowel. The presence of simple diarrhea for many months after operation need not, however, be considered as evidence of recurrence for it occurs in many patients who otherwise show no evidence of disease, have gained weight, feel well, and who show no roentgenological changes.

The case report below is given in considerable detail, because of the unusually widespread involvement of his intestinal tract, and because the patient, closely followed in Army hospitals for over a year, illustrates very graphically the classical picture of the onset and progress of this disease, with all its diagnostic and therapeutic trials and pitfalls.

CASE REPORT

Male, white, age 22, admitted to Fletcher General Hospital, August 10, 1943, with a diagnosis of diarrhea, acute, severe, type and cause undetermined. He had always enjoyed good health until February 1943, eight months after entering active military service, when he began to have diarrhea of three to five watery bowel movements daily, associated with right lower quadrant cramps, weight loss and fever. The pain occurred about 20 to 30 minutes after eating and was usually relieved shortly after his bowels moved. He reported on sick call on numerous occasions, but was not hospitalized owing to the fact that the diarrhea was not very severe. In April 1943, he began to have increased diarrhea and abdominal cramps and after two weeks without relief was admitted to the local station hospital, where with bland diet and rest he improved in two weeks and was discharged back to duty.

After two days on duty, his pain and diarrhea again recurred and he was readmitted to the hospital May 12, 1943. At this time more extensive studies were done. He was found to be running a low grade fever up to 101° F. Stool examinations showed many red blood and pus cells, but no gross pus or blood. No specific organisms or amebae were found in the stool cultures, but blood agglutination titers for Flexner Y and Shiga organisms were positive in 1 to 320 dilutions on two occasions. Sigmoidoscopy was performed twice and showed an edematous, red mucosa which bled easily, but no definite ulceration. Roentgen-rays of the upper intestinal tract were negative except for a mildly irritable duodenal bulb. Three barium enemas were performed. The result of an enema on May 18, 1943, showed no gross filling defect or obstruction in the large bowel. The barium in the descendens had a peculiar granular appearance suggesting the possibility of superficial ulceration or edema of the mucosa.

The sigmoid was definitely tender to palpation. A repeat barium enema on July 5, 1943, six weeks later, showed no gross filling defects of the large bowel. The mucosal pattern of the transverse colon and descendens was slightly irregular and the cecum was spastic. Study of the ingested meal showed the head of the barium column to have reached the descendens in four hours. The distal 10 cm. of the ileum and the cecum were very spastic and tender to palpation. These findings were considered compatible with regional enteritis. A third barium enema on July 20, two weeks later, disclosed no evidence of gross filling defect. The entire large bowel and especially the cecum was quite irritable. Owing to this irritability the cecum could not be properly filled at the time. The post evacuation film showed rather deep mucosal folds in the transverse colon, but was otherwise not unusual.

In retrospect, it would seem that on the basis of these findings, a diagnosis of regional ileocolitis involving the terminal ileum and the cecum and possibly other portions of the colon could have been made with considerable confidence. However, although the diagnosis was mentioned in a final summary, the evidence was not considered sufficient to make a positive diagnosis at that time. While in the hospital, the patient was treated with low residue diet, paregoric and kaomagma, and a course of sulfaguanidine without obtaining any marked improvement.

On July 22 the patient was transferred to another hospital. Here no additional information was obtained, except that the patient continued to run a low grade temperature, showed a persistent leukocytosis of about 11,000 white blood cells, and continued to have diarrhea and abdominal pain. The examining officers at this hospital were impressed with the patient's nervousness and anxiety, and considered the possibility of his diarrhea being of psychogenic origin associated with a vitamin deficiency. The patient was subsequently transferred to Fletcher General Hospital August 10, 1943.

On admission to this hospital the medical consultant suspected, primarily, terminal granulomatous ileitis and secondarily ulcerative colitis because of the chronic diarrhea of six months' duration, low grade fever, loss of weight and the presence of a soft, palpable mass in the right lower quadrant. The previously described sigmoidoscopic findings were confirmed. A gastrointestinal roentgen-ray examination and barium enema were done on August 11 and repeated on August 17 for confirmation. The colon filled readily with the opaque enema and was normal down to the region of the cecum. The cecum distal to the ileocecal valve appeared somewhat conical in shape and its margin was somewhat irregular. The most significant finding was a very smooth tubular appearance of the distal eight centimeters of the ileum which was somewhat narrowed and showed loss of the normal mucosal pattern (figure 1). The impression was expressed that we were probably dealing with a non-specific ileitis showing involvement of the cecum. The five hour film of the gastrointestinal series showed similar changes in the terminal ileum. The fluoroscopic examination at the same time demonstrated irritability of the terminal ileum and cecum. The barium enema on August 17 disclosed that the distal ileum showed the same appearance as previously described and that fluoroscopically the cecum was irritable and slightly deformed (figure 2). On one of the films with the distal ileum almost empty, there was a definite distortion of the mucosal pattern. These changes were considered diagnostic of terminal ileitis involving approximately eight centimeters of the distal ileum and the cecum.

On the basis of these findings, the diagnosis of terminal ileitis with involvement of the cecum and ascending colon was established. Surgical consultation was re-

Fig. 1. (*above*) Progress meal discloses the smooth tubular appearance of the distal 8 cm. of the ileum, with loss of normal mucosal pattern.

Fig. 2. (*below*) Barium enema shows similar involvement of the terminal ileum, as in figure 1. Arrows indicate the saw-tooth appearance of the mucosa of the proximal transverse colon suggestive of ulcerative involvement.



quested, the diagnosis was confirmed and a wide resection of the ileum and ascending colon was advised.

Operation was performed by Lt. Col. O. E. Nadeau on August 23, 1943. The distal 10 or 12 centimeters of the terminal ileum, the cecum and the ascending colon were involved in an indurated inflammatory process typical of regional ileocolitis. A lesser degree of inflammation extended along the transverse colon to its mid portion and along the proximal portion of the ileum for about 12 inches, associated with marked enlargement of the regional mesenteric lymph nodes. A resection was carried out in which about 18 inches of ileum, the entire cecum and ascending colon and half of the transverse colon were removed. A direct primary anastomosis between the ileum and the remaining distal end of the transverse colon was performed.

The pathological examination of the operative specimen revealed the typical macroscopic and microscopic picture of regional ileocolitis. The following detailed description of the gross and microscopic findings illustrate the pathological basis of this disease.

Macroscopic. Specimen was a portion of large and small bowel consisting of 38 cm. of ileum and 42 cm. of ascending colon. There was considerable engorgement of the serosa throughout and a moderate number of small pin point size, white nodules studded the surface of the cecal peritoneum. Many large, discrete, firm lymph nodes were present in the mesentery especially in the region of the ileo-cecal valve. Longitudinal section of the large bowel revealed thickening of the wall due to fibrosis and edema with increase in consistency. There were multiple, small, pin head size superficial areas of erosion studding the colon mucosa extending to the distal end of the preparation, but present in larger numbers in the region of the cecum. There were many large superficial as well as deeper ulcerations ranging up to the size of a dime which had a thick wall, a red, smooth, granulating base, were of variable size and shape, and were often confluent. A moderate amount of exudate covered the floor which could be washed away readily. The ulcers were somewhat serpiginous and undermined in some places (figure 3). The ulcerations appeared to be as numerous in the distal end as in the proximal end of the resected bowel. The mucosal folds of the large bowel were coarse and spongy, thickened, thrown up and stood out very prominently. The sub-mucosa was thickened and scarred, especially in the region of the ileo-cecal valve. The mucosa of the ileum, in contrast to that of the ascending bowel, did not show any ulcerative changes, other than very rare, superficial, pin point size erosions. The characteristic change here was the marked, nodular, pebble-grain appearance of the mucosa and accompanying edema and thickening of the wall of the distal 7.0 cm. of small bowel. Proximal to this region no areas of ulceration, follicular hyperplasia, stenosis, or scarring were noted; the transverse folds were somewhat thicker but not strikingly so. The lymph nodes were soft, moist, red-brown on cross section and revealed no areas of caseation.

Microscopic. Many sections taken from old indurated, as well as comparatively young and fresh lesions from the colon revealed the basic pathologic change to consist of a chronic, inflammatory granulomatous tissue reaction characterized by focal accumulations of round, large and small monocyctic cells, frequently surrounding a central core of epithelioid cells and often possessing a variable number of Langhans giant cells (figure 4). These granulomata were usually seen in the sub-mucous layer, but they were also present in the subserosal regions as well as infrequently between the muscle bundles. In many sections these foci were identical with tubercles in appearance, whereas in others this resemblance was not as apparent. Here the giant cells resembled those found in foreign body granuloma because of the absence of typical peripheral nuclear arrangement, and the presence of a lesser number and more disorderly arrangement of the nuclei. Caseation was usually absent and there appeared to be a larger number of polymorphonuclears present than in tubercle follicles.



FIG. 3. (*above*) Gross specimen of cecum discloses serpiginous, flat, undermined, or punched-out ulcerations of the mucosa, possessing a dark discolored floor covered by fibrino-purulent exudate.

FIG. 4. (*below*) Photomicrograph discloses the granulomatous tissue reaction comprising epithelioid and Langhans' giant cells surrounded by many lymphocytes (560 \times).

The ulcerations usually revealed a floor composed of dense, chronic, unspecific granulation tissue which was quite vascular and which was composed of lymphocytes, fibrocytes, and plasma cells. Eosinophiles were present in variable numbers throughout. Sometimes these lesions were superficial and did not penetrate through the lamina propria, whereas in the older ulcers, penetration through the muscularis mucosa was seen with concomitant fibroblastic proliferation and scarring and dense granulation tissue (figure 5). The ulcers here were seen to be undermined, especially toward the distal end and sloping at the proximal end, in marked similarity to chronic peptic ulcers. Edema was very extensive in some places; in other areas, dense induration of the submucosa was the predominating change (figure 6). Sections through the ileum revealed no striking ulcerative or granulomatous changes, although there was thickening of the wall. Examination of the mesenteric lymph nodes disclosed a striking focal, tubercle-like granulomatous reaction in the peri-adenomatous tissues. Here the resemblance to tuberculosis was again very strong, but again, no caseation was noted and frequently but less often, the giant cells mimicked those seen in foreign body reactions. The lymph nodes revealed marked lymphoid hyperplasia, the follicles being large and numerous. The sinuses were swollen and filled with a coagulated albuminous exudate containing many large monocytic and plasma cells, while the reticulum cords were thickened and very prominent. In other nodes, the tissue seemed to be composed mainly of sheets of densely packed lymphocytes.

Stool examinations for tubercle bacilli by smear, culture, and guinea pig inoculation were consistently negative. Cultures of bowel surface and ulcers on EMB, and desoxycholate citrate revealed no organisms of the *Salmonella* or *Shigella* groups. The tissue reaction resembled that of tuberculosis but many points of difference existed. The giant cells were usually more like those seen in foreign body granulomata and caseation was consistently absent. Neutrophils and round cells were seen in the epithelioid core in larger numbers than were usually present in tubercles. The inability to identify tubercle bacilli made it difficult to substantiate a diagnosis of tuberculosis. The pathologist thus was faced with the differential diagnosis between: (a) Regional colitis (the counterpart of regional ileitis or Crohn's disease) and (b) tuberculosis of the ascending bowel. It was felt that the former was the most likely diagnosis.

DISCUSSION

The patient made an excellent recovery from his operation and during the next three months gained weight rapidly and felt and looked well. However, he still complained of infrequent diarrhea and abdominal cramps at times. A check-up barium enema on October 13 showed some irregularity of the mucosal pattern of the proximal 10 cm. of the transverse colon and of the extreme distal portion of the ileum (figure 7). The impression was that this indicated recurrence of a granulomatous and probably ulcerative process in the colon and possibly in the terminal ileum.

On November 24 the patient had an attack of sharp right sided abdominal pain and began to run an intermittent fever up to 103° and 104° F. In spite of bed rest and a course of sulfadiazine, followed by a course of sulfaguanidine treatment, the fever and abdominal symptoms continued, associated with considerable tenderness in the right lower abdomen. Another barium enema done on December 4 showed no change in the picture of the large bowel, but showed a coarsened and fuzzy mucosal pattern of the distal 12 to 15 cm. of the ileum. On December 21, the patient had an acute attack of pain in the lower right chest and shortly thereafter developed fluid in the right pleural cavity. He again began to run a high temperature, together with increased tenderness in the right

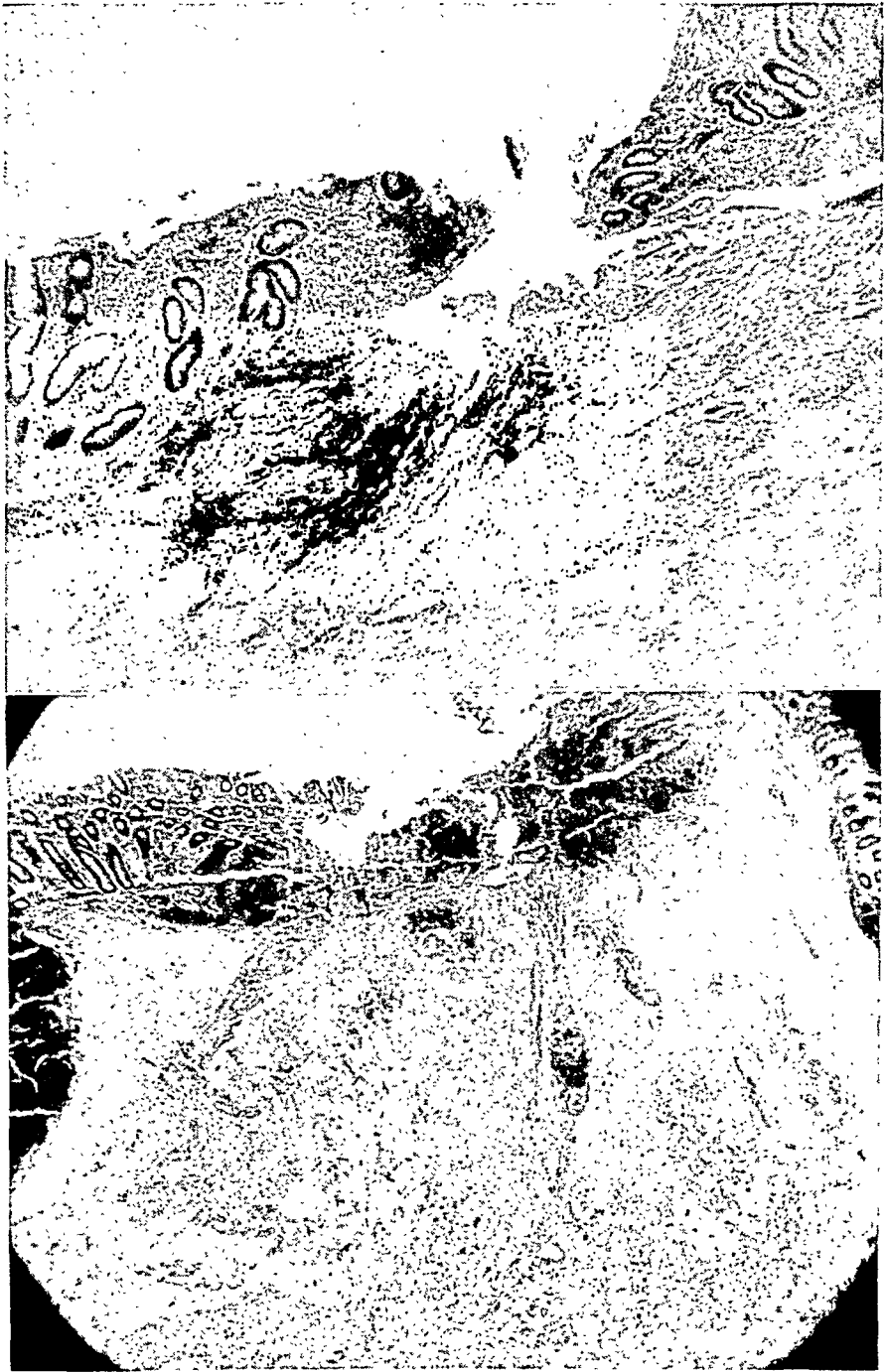


FIG. 5. (*above*). Photomicrograph demonstrates the penetrating funnel-shaped ulcer. It exhibits the characteristic undermining, granulomatous reaction and involvement of the submucosa ($70\times$).

FIG. 6. (*below*). Photomicrograph of a chronic ulcer demonstrating marked induration and fibrosis of the submucosa ($26\times$).

abdomen. Marked elevation of the right diaphragm was noticed and it was felt that the patient might well have a subdiaphragmatic abscess secondary to infection around the anastomosis of the ileum and transverse colon. On December 29, exploratory laparotomy was performed. There was no evidence of infection around the anastomosis and no subdiaphragmatic abscess. There was a moderate amount of induration and edema of the terminal ileum and the proximal por-



FIG. 7. Barium enema performed seven weeks after intestinal resection shows marked irregularity of the mucosal pattern of the transverse colon and terminal ileum at the site of their anastomosis. Arrows indicate ulcerated involvement with irritability and spasm. Dotted line at A represents stump of terminal ileum.

tion of the transverse colon confirming roentgen-ray findings. Many minute nodules were found on the serosa of the terminal ileum which had the appearance of typical tubercles. Two enlarged lymph nodes were removed for biopsy. It was decided not to carry out any further resection of the bowel at this time, because the presence of the tubercles raised the question as to whether the underlying condition might after all be tuberculosis. The fluid in the right chest was later determined to have been caused by a small pulmonary infarct.

Following the second operation, it was decided to treat the patient as if he had tuberculosis of the intestine and peritoneum while waiting for the report of the guinea pig inoculation of the diseased glands. Accordingly, he was kept at absolute bed rest for six weeks, given daily exposures to ultraviolet ray and large doses of cod liver oil by mouth. Within a few days after commencement of this treatment, the patient's temperature became normal, his abdominal pain disappeared entirely, and although his bowel movements were still liquid, there were no abdominal cramps associated with them and the patient gained 20 pounds in weight. After four weeks of further observation in the hospital, he was discharged to a veterans' hospital near his home with the recommendation that he should be kept under observation for a period of two years and should be kept for several months on a restricted physical regime with continuation of the cod liver oil by mouth and daily exposure to ultraviolet or sunlight.

The final report of the guinea pigs inoculated with lymph node material was negative for tuberculosis. A careful reëxamination of the sections removed from the cecum, ileum and mesenteric lymph nodes also failed to reveal any evidence of tuberculosis, although many features, such as the small tubercles on the serosa of the cecum and the lymphocytic infiltration and giant cells in the submucosa were very similar to the changes seen in tuberculous processes. Several sections were sent to the Army Medical Museum for examination and the following report returned: "In our view the diagnosis of distal or regional ileitis confined to the cecum is quite acceptable in this case. The histologic picture conforms to that commonly encountered in regional ileitis. The diagnosis is further supported by the negative results from the guinea pig and negative results of other examinations for acid fast bacilli."

In reviewing the case at the time that the patient was discharged from this hospital, the question was raised as to the ultimate prognosis. In spite of a rather wide radical resection at the first operation extending 12 inches above the obviously diseased part of the ileum (confirmed by later examination of the specimen) and several inches beyond the involved portion of the transverse colon, this patient developed a local recurrence and spread of the disease from the site of anastomosis of the resected bowel within a few weeks after the resection. This indicated to us that not enough bowel had been removed. Further resection was considered at the time of the second operation but wide removal of all tissue which was suspected of being even slightly involved would have meant resecting the entire remaining colon and ileum up to the lower jejunum. The response of the patient to ultraviolet radiation, cod liver oil and the general regime of treatment usually followed in cases of tuberculous peritonitis was so satisfactory that it was felt this type of treatment should be continued.

Since discharge from this hospital in March 1944, the patient has passed out of our control and we do not know how faithfully he carried out the advice for continued ultraviolet radiation and restriction of physical activity. However, we do know that he had an acute episode of diarrhea and fever in June 1944 with abdominal pain which was treated by his physician by ultraviolet radiation and bed rest (which he apparently had not been getting previously). He showed temporary improvement on this regime but later had more fever and in August 1944 was admitted to a civilian hospital in Boston, where a diagnosis of recurrent regional enteritis was made. Roentgen-rays there showed further progression of the disease since March 1943, as evidenced by narrowing of the

lumen and mucosal changes in the remaining portion of the ileum. The patient was placed on intensive vitamin therapy and given 30,000 units of penicillin daily. After 30 days in the hospital he became afebrile and began to gain weight and have normal bowel function. He was advised to go south, probably to Florida, for prolonged rest and continued exposure to sunlight.

SUMMARY

1. A case of "regional ileitis" (granulomatous ileocolitis) involving the ileum, cecum, ascending colon, and transverse colon, is reported in a soldier 22 years old.

2. The case illustrates particularly well most of the classical features of regional ileitis including the possible etiological relationship to bacillary dysentery and the marked clinical and histologic similarity to tuberculosis. The failure to respond to usual medical treatment, such as high caloric, high protein diet, bowel sedation and sulfaguanidine medication and the tendency to recurrence even after radical surgical resection is discussed.

3. The observation was made that marked clinical improvement occurred when the patient was treated intensively with ultraviolet radiation. The effect of this treatment was temporary, however, since the patient is reported to have had symptoms of recurrent activity within six months after discharge from the hospital.

BIBLIOGRAPHY

1. CROHN, B. B., GINZBURG, L., and OPPENHEIMER, G. D.: Regional ileitis, Jr. Am. Med. Assoc., 1932, xcix, 1323.
2. BOCKUS, H. L.: Gastro-enterology, Volume II, 1944, W. B. Saunders Company, Philadelphia, p. 159.
3. RAVDIN, I. S., and JOHNSTON, C. G.: Regional ileitis: a summary of the literature, Am. Jr. Med. Sci., 1939, cxviii, 269.
4. FELSEN, J.: New concepts of bacillary dysentery; its relationship to non-specific colitis, distal ileitis and non-specific granuloma, Am. Jr. Digest. Dis. and Nutr., 1936, iii, 86.
5. MARSHALL, S. F.: Regional ileitis: surgical management and results of operation, Surg. Clin. North Am., 1943, p. 873.

SHORT P-R INTERVAL WITH PROLONGATION OF QRS COMPLEX AND MYOCARDIAL INFARCTION *

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THE increasing number of case reports of the Wolff-Parkinson-White syndrome has served to emphasize the need for reappraisal of the clinical aspects of this entity.

Early descriptions associated the electrocardiographic anomaly of a short P-R interval, wide aberrant QRS complex with young, healthy males not having organic heart disease. The tendency still persists to regard heart disease occur-

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ring in the presence of this syndrome as coincidental. However, the benignity of the syndrome has been challenged by one death reported by Wood et al.¹ Anatomical studies of the heart of this patient who died during an attack of paroxysmal tachycardia demonstrated an auriculoventricular accessory pathway for the aberrant conduction producing the characteristic electrocardiographic abnormalities.

Recent case histories have continued to reiterate the occurrence of the syndrome in healthy youths but paradoxically emphasize the presence of cardiac symptomatology or other stigmata of ill health of many years' duration.

Among these reports there have been noted also several episodes of paroxysmal ventricular tachycardia. It is of value to recall that in a study of ventricular paroxysmal tachycardia based on 36 studies collected from 60,000 electrocardiograms, organic heart disease was present in all but one case.² The most frequent precipitating factor, next to digitalis intoxication, was myocardial infarction.

Attention has been directed to the possibility of error in the diagnosis of acute coronary episode as a complication of the syndrome of auriculoventricular accessory pathway.^{3, 4}

The purpose of this paper is to report a case of myocardial infarction complicating the Wolff-Parkinson-White syndrome without tachycardia.

CASE REPORT

The patient, a white male of 33 years who had served two years and five months in the Infantry, was admitted to the Station Hospital September 19, 1944, complaining of increasingly severe precordial pain and nocturnal dyspnea of two days' duration preceded by mild sore throat, rhinorrhea and generalized malaise present since September 15, 1944. The soldier had been on extremely arduous and prolonged duty throughout the hurricane of September 14, 1944.

The family history offered no pertinent data. There was no past history of diphtheria, rheumatic fever or rheumatic equivalents; infrequent convulsive episodes occurred from infancy to age 10. Two weeks prior to present admission the soldier had been a patient in this hospital for treatment of chemical conjunctivitis. Physical examination at this time was otherwise essentially negative as were routine laboratory studies of the blood and urine. There was no history of weakness, tachycardia, palpitation, dyspnea or "wheezing cough." Throughout his military service the soldier had never reported on "sick call." His personal habits were moderate.

Physical examination on the evening of admission was entirely negative except for the presence of rhonchi and sibilant râles in all lung fields particularly at the bases. The blood pressure was 130 mm. Hg systolic and 72 mm. diastolic. The heart rate was 80. In view of the history of hurricane exposure and the lung findings the patient was admitted to the Respiratory Section.

Detailed examination by the allergist revealed no significant skin sensitivities; eye, ear, nose and throat examinations by consultant staff were reported as within normal limits.

Roentgenograms of the chest, September 23, 1944 disclosed no abnormalities of the lungs or heart.

The patient continued to complain of moderate but persistent precordial distress which became less intense since hospitalization, even while on semi-ambulatory routine. However, it was evident that the asthmatic râles were often absent throughout the day, only to appear on retiring. The patient had constantly insisted that his dyspnea and wheezes occurred at this time for which reason he disliked going to bed. Routine symptomatic therapy including subcutaneous epinephrine failed to produce

expected clinical improvement. On October 2, 1944, patient was transferred to the General Medical Section for further study.

At this time physical examination disclosed no noteworthy findings. The lungs were clear and the heart apparently normal.

Roentgen-ray examination of the heart and lungs on this date, October 2, 1944, was reported as essentially negative.

The hemogram was normal—white blood cells 10,450; polymorphonuclears 76 per cent; lymphocytes 23 per cent; eosinophiles 1 per cent. Hemoglobin 82 per cent (11.8 gm.).

The electrocardiogram showed the features of the short P-R, wide QRS abnormality. The record resembled bundle branch block of the common discordant type. The rate was 75 and regular. The P-R interval was 0.08 sec.; the QRS complex was prolonged to 0.12 sec. and the classical slurring of the ascending limb of R was present in all the limb leads. ST_2 was slightly depressed; ST_3 was isoelectric and T_3 inverted and shallow (1 mm.); RT_4 was elevated 2 mm. and T_4 was upright and large, 7 mm. (figure 1).

On the evening of October 5, 1944 the patient, who had been on ambulatory convalescent routine and apparently well except for constant unexplained precordial distress, suddenly experienced severe retrosternal pain and vertigo while sitting at his bedside and slumped to the floor in syncope. Immediately noisy rattling breath sounds were audible at a distance. The patient regained consciousness in three to five minutes, was put to bed by attendants and epinephrine administered by the nurse without, however, affecting the above lung signs. The patient was in profound shock; dyspnea was severe; the color ashen and the skin cold and moist. The heart sounds were of poor quality and muffled by the respiratory rattle. The rate was 110 mm. Hg systolic and the diastolic pressure could not be determined satisfactorily. The lungs exhibited coarse, bubbling râles which were diffusely present but most marked over the bases.

The patient responded slowly but favorably to subcutaneous morphine sulfate 0.03 gm., intravenous aminophyllin 0.3 gm. and oxygen.

The electrocardiogram taken during the acute episode showed a regular rhythm with a rate of 100. The P-R, QRS relationships were unchanged. However, RT_1 was now depressed 1 mm. and bowed down; T_1 was smaller. Depression of ST_2 was accentuated. Lead III now revealed an upright T of 2 mm. The changes in RT_1 - T_4 were most marked. RT_{4-t} was now slightly depressed in marked contrast to the elevation of 2 mm. in the initial record of October 2, 1944. The T_4 waves were much smaller and suggested the M shape pattern occasionally seen in coronary insufficiency. These electrocardiographic changes were interpreted as indicating a type of acute coronary insufficiency (figure 2).

The following morning, October 6, 1944, the white blood cells numbered 17,950; polymorphonuclears 84 per cent, lymphocytes 16 per cent. Hemoglobin 88 per cent (12.7 gm.). The urinalysis was normal chemically and microscopically.

Roentgenogram of lungs and heart was essentially negative.

It was felt that this dramatic episode represented sudden left ventricular failure and cardiogenic shock precipitated by acute coronary insufficiency.

The favorable response to oxygen and supportive therapy prompted the discontinuance of digitalis, October 7, 1944, after a total of 6 cat units had been given in 36 hours in order that electrocardiographic confusion might be avoided. The temperature reached a peak of 104° the evening of October 6, 1944 but subsided to normal by October 11, 1944.

The clinical course remained uneventful thereafter except for the ever present dull precordial pain and rare asthmatic seizure, usually nocturnal.

Roentgenogram of lungs and heart, October 9, 1944, was again negative.

Blood urea nitrogen and chlorides were normal. Blood culture was negative.

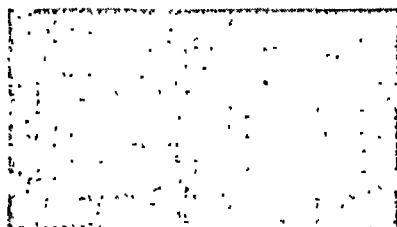
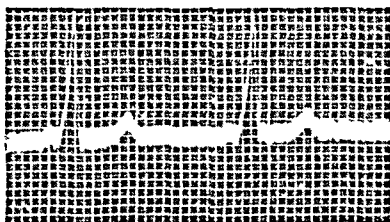
Serial electrocardiograms had shown return to control tracings of October 2, 1944 by October 17, 1944.

On October 21, 1944 the patient experienced another exacerbation of precordial distress accompanied by pulmonary edema. The electrocardiogram taken during this acute episode showed regular rhythm with rate of 100. RT_1 was now depressed 2 mm.; ST_2 was depressed 1.5 mm. T_3 was diphasic to inverted (figure 3). The chest

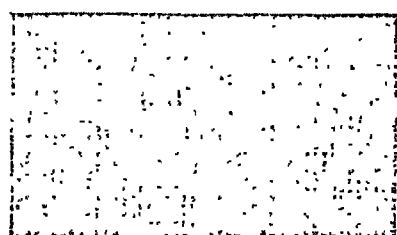
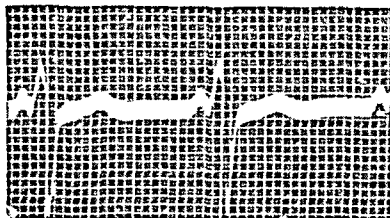
Oct. 2, 1944
Control

Oct. 5, 1944
Acute Episode

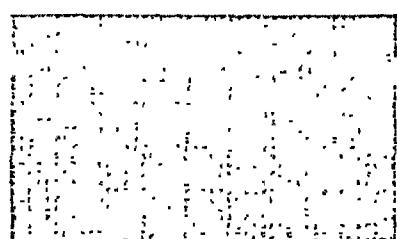
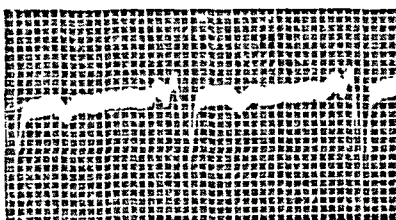
Lead I



Lead II



Lead III



Lead IV

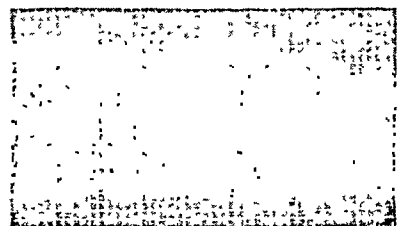
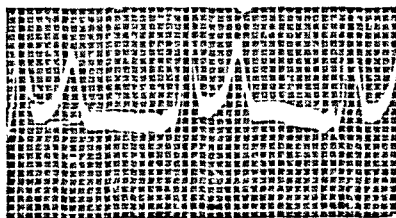


FIG. 1.

FIG. 2.

lead was not obtained. Again these changes were regarded as depicting acute coronary failure.

The electrocardiogram of November 1, 1944 showed these evolutionary changes. RT_1 was slightly depressed; T_2 tiny and upright; T_3 was coved and deeply inverted, 3 mm. ST_{4-6} was again elevated to 2 mm. and T_4 had increased in amplitude to 11 mm. (figure 4).

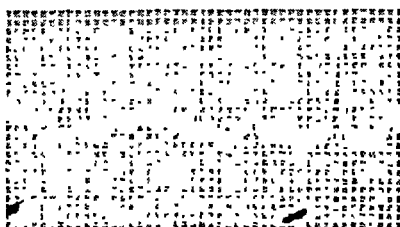
The sedimentation rate of October 22, 1944 was reported as 24 mm. (normal 10). The white blood cell count and differential smear were normal.

Following the second acute seizure the patient developed a definite anxiety state. Hyperventilation studies with electrocardiograms and psychosomatic evaluation by the Neuro-Psychiatric Section disclosed no contradictory data.

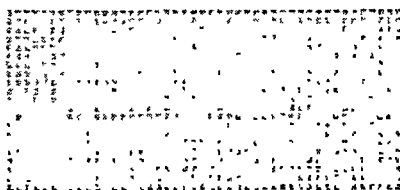
Oct. 21, 1944
Convalescent

Nov. 1, 1944
Acute Episode

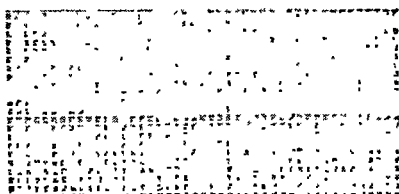
Lead I



Lead II



Lead III



Lead IV

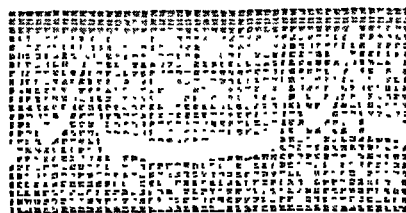
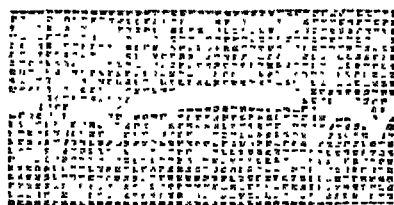
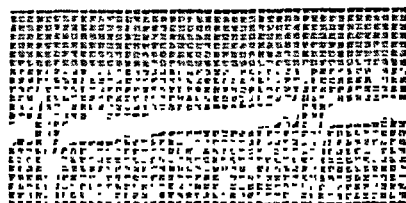
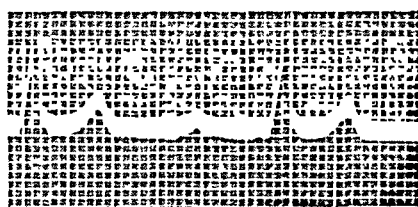


FIG. 3.

FIG. 4.

COMMENT

This case presented the electrocardiographic features characteristic of the Wolff-Parkinson-White syndrome. It differed, however, from the usual clinical entity in that paroxysmal tachycardia was never observed throughout the period of study and secondly that two acute episodes strongly suggesting coronary failure and myocardial infarction occurred.

The first attack of severe precordial pain, shock, and pulmonary edema occurring October 5, 1944 was indicative of acute coronary insufficiency or failure associated with myocardial infarction. The possibility of infarction was enhanced by the objective findings of fever, leukocytosis, and increased erythrocyte sedimentation rate. The electrocardiographic serial changes give evidence of coronary insufficiency. It is recognized that in the presence of electrocardiographic patterns of intraventricular block the coronary contour will be obscured, the resulting curve being a composite of the varying influences acting upon it.^{5, 6} Appreciation of this restriction must guide the significance given to the electrocardiographic changes in this case. The spontaneous variability of contour of the T wave has been emphasized. Review of the protocols and tracings available to us indicates that the T wave variations were induced by exercise, postural changes or other procedures calculated to produce displacement or torsion of mediastinum or vagal effects and do not indicate that significant T wave changes occur when standard electrocardiographic technic is employed.

The ST-T changes in the tracings of the acute seizures of October 5, 1944 and October 21, 1944 undoubtedly comprise the pattern of coronary insufficiency. The final records demonstrate that the T waves have not returned to the measurements present in the control record of October 2, 1944 but rather, continue to suggest the coronary contour.

A recent report of Wolff-Parkinson-White syndrome simulating myocardial infarction⁴ attributed the symptomatology and electrocardiographic changes entirely to the "relatively benign" syndrome. It is interesting to note that the tracings reproduced in this paper show definite evolution of the RT-T combination as usually occurs in posterior myocardial infarction. The history of this patient, clinical course, accentuated as it was by a not uncommon anxiety state, and finally serial changes in the electrocardiogram do not permit the ruling out of coronary insufficiency.

Similar misgivings are contained concerning case 4 reported by Palatucci and Knighton.³ These authors denied the diagnosis of coronary occlusion, made by two other observers, in a patient whose history and electrocardiographic changes pointed strongly to coronary failure. Their principal objection to the diagnosis of an acute coronary episode rested on the absence of collateral findings such as increased sedimentation rate and leukocytosis. Again it is of interest to note that serial tracings never returned to the pattern of the control record.

Both of these cases exhibit insufficient consideration of anamnestic data and electrocardiographic changes which under ordinary circumstances would be of paramount aid in diagnostic and clinical appraisal.

The occurrence of coronary occlusion without myocardial infarction already has been well established.⁷ French and Dock⁸ have demonstrated the presence of old myocardial scars in 59 per cent of 80 fatal cases of coronary disease in soldiers aged from 20 to 36. Master has discussed the clinical pictures of coronary insufficiency and coronary occlusion. Although the diagnosis of occlusion or coronary insufficiency without infarction cannot be proved during life, inflexible insistence upon objective or collateral findings may be contrary to clinico-pathologic data.

SUMMARY

A case is reported in which a diagnosis of myocardial infarction was made on a patient having a history of severe precordial pain, shock, pulmonary edema

and an electrocardiogram characterized by short P-R interval associated with prolonged QRS.

The diagnosis is justified by occurrence at rest of sudden, severe precordial distress and collapse accompanied by electrocardiographic serial changes, fever, leukocytosis and increased erythrocyte sedimentation rate.

Despite the emphasis on the incidence of this unusual abnormality, short P-R-prolonged QRS, in apparently healthy youths, warning is restated that although the syndrome may be regarded as a rare normal variant, all such cases should be viewed suspiciously and critically.

Conservative opinion must conclude that the possibility of coronary involvement cannot be ruled out in cases having history and findings as reported herein.

BIBLIOGRAPHY

1. WOOD, F. C., WOLFERTH, C. C., and GECKLER, G. D.: Histologic demonstration of accessory muscular connections between auricle and ventricle in a case of short P-R interval and prolonged QRS complex, *Am. Heart Jr.*, 1943, xxv, 454.
2. WILLIAMS, C., and ELLIS, L. B.: Ventricular tachycardia, *Arch. Int. Med.*, 1943, lxxi, 137.
3. PALATUCCI, O. A., and KNIGHTON, J. E.: Short P-R interval associated with prolongation of QRS complex; a clinical study demonstrating interesting variations, *Ann. Int. Med.*, 1944, xxi, 58.
4. EICHERT, H.: Wolff-Parkinson-White syndrome simulating myocardial infarction, *Ann. Int. Med.*, 1944, xxi, 907.
5. LIEBERSON, A., CHASNOFF, J., and GOLDBLOOM, A. A.: Clinical studies in electrocardiography. IV. The value of the electrocardiogram in coronary thrombosis, with special reference to localization of infarct, *New York State Jr. Med.*, 1941, xli, 2032.
6. KATZ, L. N.: *Electrocardiography*, 1943, Lea & Febiger, Philadelphia.
7. BLUMGART, H. L., SCHLESINGER, M. J., and ZOLL, P. M.: Angina pectoris, coronary failure and acute myocardial infarction, *Jr. Am. Med. Assoc.*, 1941, cxvi, 91.
8. FRENCH, A. J., and DOCK, W.: Fatal coronary arteriosclerosis in young soldiers, *Jr. Am. Med. Assoc.*, 1944, cxxiv, 1233.

EDITORIAL

STREPTOMYCIN

"THE story of streptomycin is the story of a search for an antibiotic substance capable of exerting a bacteriostatic and bactericidal effect upon gram-negative bacteria, a substance active against these organisms not only in the test tube but also in the animal body, yet not very toxic nor exerting otherwise undesirable effects upon the body, a substance not inactivated by the body fluids and, therefore, offering chemotherapeutic potentialities." Thus runs the opening statement in the review of *Streptomycin* by Waksman and Schatz,¹ who have played such an important rôle in furnishing this new, highly potent antibiotic agent to the medical world.

It is difficult to realize that a mere ten years ago the sulfonamide drugs were added to our therapeutic armamentarium, thereby revolutionizing the chemotherapy of bacterial infections. During the next few years the clinician was confronted with a series of sulfonamide compounds, each of which was acclaimed as superior to its predecessor. And just about the time the clinician had learned the hard way of the potentialities and dangers of the sulfonamide drugs through therapeutic triumphs and therapeutic deaths, the "wonder-drug" penicillin was thrust upon his lap as a remedy more potent and less toxic than the sulfonamide compounds. Now that penicillin is readily available—although still expensive—it is distressing to observe the indiscriminate use of this drug in practically every patient who develops an elevation of temperature.

Granting that the sulfonamides and penicillin are highly potent therapeutic agents against many bacterial infections, it is generally accepted that their chief value lies in the treatment of infections due to gram-positive organisms such as the streptococcus, staphylococcus, and pneumococcus. To be sure, both the sulfonamides and penicillin have proved highly effective against certain gram-negative cocci such as the meningococcus and gonococcus, while certain sulfonamides have served to suppress such gram-negative bacillary infections as acute brucellosis, colon bacillus urinary tract infections, and infections due to *Hemophilus influenzae*. However, there are many infections due to gram-negative organisms in which both the sulfonamides and penicillin proved to be relatively ineffective. It is for the treatment of such infections that streptomycin offers the greatest promise.

In 1939 Waksman and his associates in the Department of Microbiology of the New Jersey Agricultural Experiment Station at Rutgers University began to study production of antibiotic substances by microorganisms. Some thousands of actinomycetes, hundreds of fungi and many bacteria were isolated from normal soils and enriched soils, from composts, manures and

¹ WAKSMAN, S. A., and SCHATZ, A.: A review . . . streptomycin, Jr. Am. Pharmaceut. Assoc., Practical Pharmacy Edition, 1945, vi, 308.

peat bogs as well as from other natural materials. Special methods were devised for the isolation of antagonistic organisms and technics were developed for the production, isolation, and study of the active antibacterial substances. The isolation of streptomycin must, therefore, be regarded as the result of extensive surveys, detailed analyses and numerous tests in which many collaborators have participated. These studies resulted in the isolation of an actinomyces which was found capable of producing, in certain media, an antibiotic substance that apparently possessed many of the desirable antibacterial and pharmacologic properties. This substance was designated as streptomycin, the name being derived from the generic designation given to the sporulating and aerial mycelium-producing group of actinomycetes, *Streptomyces*. Characteristics of these organisms relate them to both bacteria and molds.

Crystalline streptomycin is now available which, in contrast to penicillin, is markedly stable both chemically and biologically. The pure base possesses an activity of about one unit per microgram. The action of streptomycin is generally bacteriostatic in low concentrations and bactericidal in higher concentrations. It is active in vitro against a variety of pathogenic gram-positive and gram-negative bacteria, including *Mycobacterium tuberculosis*, *Eberthella typhosa*, *Pasteurella tularensis*, *Klebsiella pneumoniae* (Friedländer's bacillus), *Brucella abortus*, *Proteus vulgaris*, *Hemophilus pertussis*, *H. influenzae*, *Pseudomonas aeruginosa*, and many others.

Studies on the absorption and excretion of streptomycin in animals have shown that this antibiotic, administered parenterally, behaves like penicillin in that both agents are rapidly absorbed and rapidly excreted in the urine. Therapeutic blood levels are easily produced by intravenous or subcutaneous injections. Oral dosage, on the other hand, results in very low blood concentrations. The toxicity of streptomycin, especially of purified preparations, was found to be extremely low. When present, it revealed itself in animals usually as a histamine-like reaction. A second toxic effect, namely fatty infiltration of the liver and occasionally of the kidneys, was especially pronounced in monkeys following prolonged administration of large doses of streptomycin. The latter type of reaction has never been observed in man even after prolonged administration of as much as 4.0 grams of streptomycin daily. Streptomycin has been administered to human beings intramuscularly, intravenously, and subcutaneously, both by intermittent injection and by continuous drip. It has also been given intrathecally, orally, and by nebulization into the tracheobronchial tree. When ingested, streptomycin is not appreciably absorbed nor is it destroyed in the intestine. This persistence and stability in the gut has been used to advantage for the treatment of typhoid patients. After parenteral administration, streptomycin has been detected in ascitic and pleural fluids in concentrations approximating the level in the blood, whereas diffusion from the blood stream into the cerebrospinal fluid is generally slight.

To date streptomycin has been administered² with highly encouraging results to patients with heretofore resistant gram-negative bacillary infections of the urinary tract, typhoid fever, tularemia, pulmonary and meningeal infections due to Friedländer's bacillus and *Hemophilus influenzae*, bacteremias due to gram-negative bacilli such as *Proteus vulgaris*, *Escherichia coli*, *Aerobacter aerogenes* and *Salmonella*, and wound infections. Furthermore there is suggestive evidence that streptomycin may prove beneficial in the treatment of acute brucellosis and tuberculosis although no definite conclusion may be drawn as yet. Although exerting some suppressive action against *Treponema pallidum*, *Borrelia novyi*, and *Leptospira icterohaemorrhagiae*, streptomycin has proved to be far less effective than penicillin in the treatment of syphilis and other spirochetal infections. Streptomycin has also proved valuable in the treatment of infections due to the gram-positive *Streptococcus faecalis* which is unaffected by sulfonamides or penicillin.

Streptomycin has a limited but definite toxicity³ for human beings. The most serious reaction is a vestibular disturbance, causing dizziness, tinnitus, ataxia, and occasionally transient deafness. This reaction has occurred after large doses have been administered over long periods; it has not been observed in cases in which only short courses of treatment (up to two weeks) have been employed. This reaction warrants interruption of drug therapy. Irritation and pain at the site of injection are common; for this reason rotating the sites of intramuscular injections is recommended. Toxic erythema and a diffuse generalized morbilliform cutaneous rash with fever and eosinophilia may occur at times after several days' administration of streptomycin. Arthralgias, myalgias, headache, nausea and vomiting, probably due to impurities, have been observed after the administration of certain batches of streptomycin. Some renal irritation, manifested by a transient increase in urinary output, hematuria, and cylindruria, has been noted following the administration of large doses.

The supply of streptomycin is limited as yet, and total allocation of the drug is now in the hands of the Civil Production Administration. It is now being allocated to the Army, Navy, Veteran's Administration, U. S. Public Health Service, and the Committee on Chemotherapeutic and Other Agents of the Division of Medical Sciences of the National Research Council. No one other than the agencies named may purchase streptomycin. No patient who receives it may pay for it; no physician is charged for it. Streptomycin for civilian use is placed in charge of the chairman of the committee of the National Research Council for distribution to those hospital physicians most competent to obtain the vitally needed information regarding the diseases which are to be investigated under this committee. The chairman, Dr. Chester Keefer,⁴ has recently published an official statement listing those dis-

² HERRELL, W. E., and NICHOLS, D. R.: The clinical use of streptomycin: a study of forty-five cases, Proc. Staff Meet. Mayo Clin., 1945, xx, 449.

³ Streptomycin. A review of current experience, Bull. U. S. Army Med. Dept., 1946, v, 531.

⁴ KEEFER, C. S.: Official statement concerning streptomycin, Jr. Am. Med. Assoc., 1946, cxxxii, 31.

eases which are at present under investigation. Any physician desiring streptomycin would do well to consult this list before requesting the drug in order to determine whether his patient is "eligible."

Streptomycin, then, is here to stay, at least until some superior antibiotic preparation comes along to supersede it. And if such a super-drug is developed, it too will in all likelihood emerge from the earth under our feet. To one with a philosophical twist, it must seem mildly entertaining to reminisce over the major advances in antibiosis during the past twenty years. Starting with the pneumococcal polysaccharide-splitting enzyme culled from a cranberry bog, we have seen gramicidin, tyrothricin, penicillin, streptothricin, and finally streptomycin "sprout" from the soil in rapid succession. At the rate things are going the bacteriologists and chemotherapists may soon supplant the sociologists as the prime supporters of the "back-to-the-soil" movement!

W. H. B.

CORRESPONDENCE

TREATMENT OF RHEUMATIC HEART DISEASE BY ROENTGEN-RAY IRRADIATION

July 8, 1946

To the Editor:

In the *Annals of Internal Medicine* for June, 1946 (p. 1039), there was published an article by Griffith and Halley entitled "The Treatment of Rheumatic Fever by Roentgen-Ray Irradiation." These authors referred to a series of four papers published by us between 1926 and 1933, and reached conclusions apparently at variance with ours. Our last paper, "Roentgen Therapy of Active Rheumatic Heart Disease: A Summary of Eleven Years' Experience" (*Am. Jr. Med. Sci.*, 1937, cxciv, 597), was not cited.

A comparison of material and method readily serves to indicate the reasons for the discrepancies. They evidently were concerned with the general manifestations of rheumatic fever rather than primarily with its cardiac aspects. Their cases were classified as acute fulminating, subacute polycyclic, subacute monocyclic and subclinical. No description was given of the cardiac status of their patients. Our attention was focused on the heart.

They did not follow the technic of irradiation which we recommended. In our studies, approximately 60 r, as measured in air without back-scattering, was applied to the front of the chest, and from 100 to 125 r to the back, depending upon the depth of the patient's thorax. The object was to distribute approximately 60 r, as measured in air, throughout the heart area. The treatments were given at intervals of two weeks for four sittings. Then a period of one to three months was allowed to elapse and the series was repeated. The number of treatments given to an individual ranged from 3 to 25, with an average of 9. Twelve cases received 10 or more. In general, those receiving the larger number of treatments fared best.

To one group of patients, Griffith and Halley gave "100 r through the myocardium"; another group received the same dose through the myocardium and also over the middle and lower cervical sympathetic ganglia. This statement does not make it clear whether 100 r was the measurement in air or whether it represented an estimate of tissue dose. The treatments were given at weekly intervals for five successive weeks.

In the light of our experience, we feel justified in repeating some of our conclusions stated in 1937: (1) In a considerable number of patients irradiation therapy exerted a favorable effect upon the lesions in the heart and upon the course of the disease; (2) irradiation relieved cardiac pain in patients who did not have aortic insufficiency; (3) no harmful effects were noted; (4) cases with low-grade activity and without signs of congestive heart failure appeared to be most benefited whereas the acute cases were not improved; (5) roentgen irradiation of the heart, in the present state of knowledge concerning rheumatic fever, deserves a place as a therapeutic measure in properly selected cases of active carditis.

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REVIEWS

Diseases of the Adrenals. By LOUIS J. SOFFER, M.D. 304 pages; 24 × 15.5 cm. Lea & Febiger, Philadelphia, Pa. 1946. Price, \$5.50.

The author states in his preface that he has attempted to present the present day knowledge of both the physiology and diseases of the adrenals. He has fulfilled his purpose in all respects. After a brief description of the anatomy of the glands, the laboratory technics of value in the diagnostic survey of a suspected case of adrenal dysfunction are outlined. An interesting discussion of the physiology of the adrenal glands, with emphasis on their endocrine inter-relation, facilitates the detailed discussion of Addison's disease and the Waterhouse-Friderichsen syndrome which follows. The management of an Addisonian crisis is well presented and the author properly emphasizes the dangers of over-zealous pellet implantation in the treatment of Addison's disease.

The morbid states associated with adrenal cortical hyperfunction are grouped under the title "Adreno-genital Syndrome." This may prove misleading for those who reserve the term for the condition characterized predominantly by disturbances in sexual physiology; however, our understanding of the basic aberrations in adrenal cortical hyperfunction is still incomplete and new approaches to the problem are warranted. Perhaps the use of Talbot's method of assaying 11-Oxycorticosteroids, used more widely, will lead to a clarification.

The bibliographies at the end of each chapter are excellent, and, whenever possible, discussions of diagnoses or therapy are effectively summarized at their conclusion.

This book will prove invaluable to any physician dealing with adrenal disorders.

J. Z. B.

Human Gastric Function. An Experimental Study of a Man and His Stomach. By STEWART WOLF, M.D., and HAROLD G. WOLFF, M.D.; Foreword by WALTER B. CANNON. 195 pages; 16 × 24 cm. Oxford University Press. 1943. Price, \$4.75.

This study of a man and his stomach should be read by every physician, practitioner, specialist and research man. It should be read by those who reject or are skeptical about the "psychosomatic approach," as well as by those who are sold on it but too often do not take the trouble to study carefully both aspects, the somatic and the psychological, and to correlate the two series of findings.

The subject of this study, a 57 year old man, presented an unusual opportunity for the investigation of the behavior of a human stomach. Tom, at the age of 9, had been operated on for an esophageal stricture resulting from drinking extremely hot clam chowder. The lumen of the esophagus could not be kept open and a gastrostomy had to be performed. "The anterior portion of the greater curvature of the stomach was brought out and sutured to the abdominal wall," but a plastic closure could not be done. Tom was "left with a defect in his abdominal wall 3.5 cm. in diameter, through which a collar of redundant gastric mucosa herniated. Thereafter, he fed himself through the artificial opening," first chewing the food in his mouth and then spitting it into a funnel with attached rubber hose that he inserted into his stomach.

The authors thus had the opportunity for prolonged close inspection of the stomach mucosa, that is of the exposed collar of the mucous membrane as well as of the interior of the stomach (by inserting a lighted anoscope).

Various functions of the stomach, as well as the behavior of the stomach mucosa under different conditions, were studied over a period of months. Tom was made attendant in the laboratory where the project was carried out. This not only had the

advantage of his being available at any time, it also afforded the opportunity of studying the man in an environment which, after a while, lost its artificiality for him and became his natural habitat.

A careful study of Tom's background and personality is presented. The behavior of the stomach, changes in blood flow, motor activity and secretion, were studied under varying conditions and influences, especially under the influence of common physical and chemical agents, and under that of various life situations and accompanying emotional states. The effect on the stomach mucosa of temperature changes, mechanical irritation, tobacco smoking, acids and antacids, various drugs ranging from nitroglycerin and atropin to pitressin and acetylcholine, was investigated. One of the important findings here was the observation that the effect of one and the same drug on the gastric mucosa varied according to the emotional condition of the subject at the time of the experiment.

"Emotionally charged situations were not experimentally induced but spontaneously occurring life problems and conflicts were utilized. . . . His reaction to each of these experiences was evaluated in the light of his personality pattern. . . . Thirty-four observations of stomach function accompanying several different affective states were made." Illustrative examples are presented.

The importance of this experimental study for the understanding of "gastritis" and ulcer formation can be deduced from the following conclusions: "Undue and prolonged acceleration of acid secretion in the stomach, however provoked, resulted in hyperemia and engorgement of the mucous membrane resembling hypertrophic gastritis. The mucosa in this state was unusually susceptible to injury, and even the most trifling traumata resulted in hemorrhages and small erosions. Ordinarily the mucosa was protected from injury by an effective coating of mucus. Loss of this protection in the face of minor traumata led to oedema, inflammatory changes, erosions, and hemorrhages. Contact of acid gastric juice with a denuded surface induced further hyperemia and acceleration of acid secretion. Prolonged contact of acid juice with a minor erosion resulted in the formation of a peptic ulcer." It is interesting to note that the ulcer thus produced in the subject over a period of four days, disappeared completely, leaving no trace of a lesion, within three days during which the area was covered with a protective petrolatum dressing.

Alterations in gastric function, paralleling emotional disturbances, fell into two categories: (1) depression of acid output, motor activity and vascularity, "associated with a reaction of flight or withdrawal from an emotionally charged situation;" (2) acceleration of these functions, associated with "a reaction of internal conflict, with an unfulfilled desire for aggression and fighting back." "Profound and prolonged emotional disturbances of this kind were accompanied by marked and prolonged increases in gastric motility, secretion, and vascularity, with reddening and engorgement of the mucous membrane, often reproducing the picture of 'gastritis'." Vasomotor changes observed in the stomach often corresponded to similar pallor or blushing of the face. There was also a correlation between the amount of activity of the stomach on one hand and the amount of talkativeness and general body activity on the other hand. "The altered gastric function," the authors conclude, "was merely a part of the whole pattern of bodily reaction," in the face of mechanical and pharmacological stimulation as well as under the influence of situational and emotional factors.

In the light of their findings, suggestions as to the clinical management of gastritis and ulcer patients are offered, which should be helpful to general practitioners, surgeons, psychiatrists and internists alike.

Diagrams and other illustrations are clear, simple and truly illustrative. The book is a remarkable example of a complex research project concisely and lucidly presented.

Men under Stress. By Lt. Colonel ROY R. GRINKER, M. C., and Major JOHN P. SPIEGEL, M.C., Army Air Forces. 484 pages; 16 × 24 cm. Blakiston Co., Philadelphia. 1945. Price, \$5.00.

This is one of the most important publications in the field of military psychiatry to appear on the market during the second World War. It is written by two psychiatrists who were connected with the Army Air Forces overseas and later with Don Cesar Hospital, an Army Air Force convalescent hospital receiving cases of war neuroses. They therefore had a chance to study reactions before and after combat and actually to follow up some men whom they had sent home. This book is the second one of the authors; their first was a study of psychologically wounded Ground Force soldiers and appeared earlier as a "restricted" military monograph. Two books make for interesting comparisons, and their differences add more to the field of psychiatric research.

The present work is clearly and interestingly written with a wealth of case material and discussion. Points of theory are carefully developed and conclusions are drawn which are sound and applicable to practical use. The authors build up their work in almost a novel form. Their thesis is that "under sufficient stress any individual may show failure of adaptation, evidenced by neurotic symptoms." War tries men as a cruel experiment and hard though it may be, "valuable lessons" can be learned about man's adaptation and applied to problems of civilian living. The authors add that the problems of the peace following the war may put as much strain on man as those of the war. With the thesis thus stated, they develop the plot by first describing the men of the Army Air Forces, their motivations, conscious and unconscious, to become fliers, and their selection physically, psychologically and psychiatrically by the army. Important conclusions as to who were capable psychiatrically of flying were obtained mostly after the test of combat. Some individuals deemed good material for combat flying developed "operational fatigue," whereas others suffering from neurosis in civilian life were able to endure a complete tour of combat duty. The next section of the book is devoted to what the environment of combat is like—how A.A.F. units are formed, their motivation to fight and how dependent morale is on the composition of the unit—each individual contributing personally to the morale of the whole and of each member. The third and fourth sections deal with the reactions to combat stress and to the return home. These sections comprise the bulk of the book and are concerned with quoting of case material, psychodynamics, and treatment. The authors make a distinction between reactions to combat based on previous neuroses and neurotic reactions of "stable" individuals to severe stress. They cannot come to definite conclusions regarding differential prognoses of the second class because of their inability to follow up enough cases. The final section is concerned with civilian applications—the importance of psychiatric understanding in general medical practice and the great need for many more properly trained psychiatrists, also the addition of new treatment procedures and further proof of some theories existing before the war and now having the benefit of mass validation. A final note of warning is issued by the authors for the treatment of the returned soldier—unless we have a program that meets his psychological needs, we stand in grave danger of political upheavals, pension armies, and other forms of sociological behavior which arise from psychological maladjustment.

This book should have a wide appeal to the psychiatrist, the general practitioner and the intelligent layman. It is theoretically sound, based on modern dynamic psychology, yet not too theoretical for those outside the field. The style is clear and has literary merit. There is some annotation but not enough to make the book ponderous or obviously scholarly. The bibliography is good, although not long.

H. W. N.

What People Are. A Study of Normal Young Men. By CLARK W. HEATH, Dept. of Hygiene, Harvard University. 141 pages; 21.5 × 14.5 cm. 1945. Harvard University Press, Cambridge, Mass. Price, \$2.00.

This little book, as stated in the preface, is a "brief introduction to the point of view of the Grant Study and the methods used in the effort to study normal human beings." It is divided into three sections, the first an explanation of the selection of subjects, the general plan of study and the methods used in examining the subjects. The subjects used were Harvard students, in their second year of college work. They were chosen for their satisfactory records both academically and in their relationship with others. They had no physical or psychological abnormalities of sufficient magnitude to warrant reporting on the college records. These boys were studied by a group consisting of a physician trained in internal medicine, a physiologist, a physical anthropologist, a psychologist, two psychiatrists and a personnel worker in charge of collecting socio-economic information.

The second and main portion of the book goes into considerable detail describing the findings of this study. According to their findings, the author has divided their subjects into three fairly well differentiated types of normal personalities and has pointed out their outstanding traits. They have found relationship between body build and personality features. Many interesting things, suggestive of correlation in other fields were brought out, but further study and follow up will be necessary before any definite statements can be made.

The third part of the book points out that further study of this group and of other groups of young men, with a view to comparing them with this selected group of young men, is desirable. It also sums up the follow-up work which has been done and which is to be continued throughout the lifetime of the participants.

The book is interesting and informative. Anyone interested in people, normal or abnormal, will find in it much of importance, together with suggestions of a new approach to finding out "what people are." It is admittedly an introduction, but one which will stimulate all who read it and cause them to await with interest further publications on the Grant Study.

R. K. G.

BOOKS RECEIVED

Books received during June are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Principles of Bacteriology and Immunity. W. W. E. TOPLEY, and G. S. WILSON. Two volumes. Vol. I, 970 pages; 24.5 × 17 cm. Vol. II, 2054 pages; 24.5 × 17 cm. 1946. Williams & Wilkins, Baltimore. Price, \$12.00.

A Textbook of the Practice of Medicine. By various authors. Edited by FREDERICK W. PRICE, M.D. Seventh Edition. 2034 pages; 23 × 14.5 cm. 1946. Oxford University Press, New York. Price, \$13.50.

Through the Stratosphere. The Human Factor in Aviation. By MAXINE DAVIS. 253 pages; 22 × 14.5 cm. 1946. The MacMillan Company, New York. Price, \$2.75.

The Early Diagnosis of the Acute Abdomen. By ZACHARY COPE, B.A., M.D., M.S. 262 pages; 22.5 × 14.5 cm. 1946. Oxford University Press, New York. Price, \$3.75.

- A Manual of Tuberculosis.* By E. ASHWORTH UNDERWOOD, M.B., B.Sc., M.D. Third Edition. 524 pages; 19.5 × 13 cm. 1945. The Williams & Wilkins Company, Baltimore. Price, \$4.50.
- Neurosis and the Mental Health Services.* By C. P. BLACKER, M.A., M.D., F.R.C.P. 219 pages; 22 × 14.5 cm. 1946. Oxford University Press, New York. Price, \$5.00.
- A B C of Medical Treatment.* By E. NOBLE CHAMBERLAIN, M.D., M.Sc., F.R.C.P. 206 pages; 19 × 12.5 cm. 1946. Oxford University Press, New York. Price, \$3.00.
- Studies in Hypertony and the Prevention of Disease.* By I. HARRIS, M.D. 114 pages; 19 × 12.5 cm. 1946. The Williams & Wilkins Co., Baltimore. Price, \$3.00.
- Autopsy Diagnosis and Technic.* By OTTO SAPHIR. Second Edition, revised. 405 pages; 19.5 × 13.5 cm. 1946. Paul B. Hoeber, Inc., New York. Price, \$5.00.
- Medical Jurisprudence and Toxicology.* By JOHN GLAISTER. Eighth Edition. 691 pages; 22 × 14.5 cm. 1945. Williams & Wilkins Company, Baltimore. Price, \$8.00.
- Psychological Medicine.* Second Edition. By DESMOND CURRAN, M.B., F.R.C.P., and ERIC GUTTMAN, M.D., M.R.C.P. 246 pages; 22 × 14.5 cm. 1945. The Williams & Wilkins Company, Baltimore. Price, \$3.50.
- Narcotics and Drug Addiction.* By ERICH HESSE, M.D.; translated by FRANK GAYNOR. 219 pages; 24 × 15.5 cm. 1946. The Philosophical Library, Inc., New York. Price, \$3.75.
- Renal Diseases.* By E. T. BELL, M.D. 434 pages; 23 × 15.5 cm. 1946. Lea & Febiger, Inc., Philadelphia. Price, \$7.00.
- The Modern Treatment of Diabetes Mellitus.* By WILLIAM S. COLLENS, B.S., M.D., and LOUIS C. BOAS, A.B., M.D. 514 pages; 23 × 15.5 cm. 1946. Charles C. Thomas, Springfield, Ill. Price, \$8.50.
- Manson's Tropical Diseases.* Twelfth Edition. Edited by PHILIP H. MANSON-BAHR. 1068 pages; 22.5 × 15 cm. 1945. Williams and Wilkins Company, Baltimore. Price, \$12.00.
- Diseases of the Retina.* By HERMAN ELWYN, M.D. 587 pages; 23.5 × 16 cm. 1946. The Blakiston Company, Philadelphia. Price, \$10.00.

COLLEGE NEWS NOTES

A.C.P. REGIONAL MEETING, PITTSBURGH, SEPT. 25

Under the Governorship of Dr. Roy R. Snowden, Pittsburgh, a Regional Meeting of the College for Western Pennsylvania will be held at the Medical Center, Wednesday, September 11, 1946.

This meeting comes in the midst of an A.C.P. Postgraduate Course in Internal Medicine under the direction of Dr. Snowden at the University of Pittsburgh, September 2-14. The Regional Meeting program also becomes a part of the course for that day. The theme of the scientific program for the Regional Meeting will be "Frontiers of Science." Dr. W. S. McEllroy, F.A.C.P., Dean of the University of Pittsburgh School of Medicine, will preside. There will be a description and demonstration of the ultra-centrifuge, electron microscope and cyclotron.

The latest knowledge of the atom and molecule, and the applicability of this knowledge in medical science will be presented by Max A. Lauffer, Ph.D., Associate Research Director, Department of Physiological Chemistry, University of Pittsburgh, and Alexander J. Allen, Ph.D., Westinghouse Graduate Professor of Engineering, University of Pittsburgh. The Annual Regional Banquet will be held, followed by short addresses by distinguished guests. Those enrolled in the course as well as all instructors will be guests of the College.

FORTHCOMING BOARD EXAMINATIONS

The next examination of the American Board of Psychiatry and Neurology will occur in December 1946 in New York. More specific information as to date and location will be given in a later issue of the Annals.

The 1946 examinations of the American Board of Radiology will be given in Chicago at the Palmer House, November 27-30, 1946.

The College has been advised that the oral examination of the American Board of Internal Medicine will be given in Chicago, October 29, 30 and 31, 1946. Candidates will note the addition of October 29 to the dates previously announced.

GIFTS TO THE COLLEGE LIBRARY

The following gifts of publications by members are gratefully acknowledged:

D. E. H. Cleveland, F.A.C.P., Vancouver, B. C., Can.—1 reprint.
Samuel Cohen, F.A.C.P., Jersey City, N. J.—2 reprints.
Samuel E. Cohen (Associate), Elmira, N. Y.—4 reprints.
Charles A. R. Connor (Associate), New York, N. Y.—1 reprint.
Lewis J. Moorman, F.A.C.P., Oklahoma City, Okla.—3 reprints.
Frederick W. Mulrow, F.A.C.P., Cedar Rapids, Iowa—2 reprints.
Sidney L. Penner (Associate), Fort Bragg, N. C.—2 reprints.
George X. Schwemlein (Associate), Cincinnati, Ohio—2 reprints.
Ramon M. Suarez, F.A.C.P., Santurce, San Juan, P. R.—2 reprints.

At the recent meeting of the American Medical Association in San Francisco, Dr. Edward L. Bortz, F.A.C.P., Philadelphia, College Governor for Eastern Pennsylvania, was elected vice-president. Dr. Olin West, who recently retired as General Secretary of the American Medical Association, was elected President-elect. Dr. Francis F. Borzell, F.A.C.P., Philadelphia, was reelected Speaker of the House of Delegates.



Dr. Edwin Joseph Cohn, 1946 Phillips Medalist, The American College of Physicians

**DR. EDWIN JOSEPH COHN RECEIVES THE JOHN PHILLIPS MEMORIAL MEDAL FROM THE
AMERICAN COLLEGE OF PHYSICIANS**

The American College of Physicians awards periodically the John Phillips Memorial Medal to a scientist of the United States or Canada, who is recognized by the Board of Regents, upon recommendation of the Committee on Fellowships and Awards, as having made the most significant contribution to research in the field of internal medicine for the immediate preceding period.

Dr. Edwin Joseph Cohn, Professor of Biological Chemistry and Head of the Department of Physical Chemistry of Harvard Medical School, and Chairman of the Division of Medical Sciences of the Faculty of Arts and Sciences, Harvard University, Boston, was chosen for the 1946 award. His citation reads as follows:

"Eminent scientific investigator, whose distinguished research on the physical chemistry of amino acids, peptides, and proteins has brilliantly elucidated the chemical interactions of biological systems and made possible the separation of the components of concentrated solutions rich in proteins, for exceptionally meritorious accomplishment in the fractionation of human plasma into purified substances of preventative and therapeutic value. Through exacting and meticulous research, fraught with the romance of new and incredibly intricate techniques of isolation, measurement and definition, in the realm of ultracentrifuges and ingenious optical systems, of streaming birefringence, diffusion constants and viscosity coefficients, of electrical charge distributions, atomic relations and ionic atmospheres, Dr. Cohn has devised and directed the partition of human plasma by physical-chemical methods and the preparation, primarily for use of the armed forces on the battle fields of the world, of at least five products possessing important clinical uses: albumin for combatting shock, isohemagglutinins for blood grouping, fibrinogen and thrombin for hemostasis, and gamma globulin for passive immunization against epidemic disease. The field of usefulness of all these new products is only beginning to be explored and is limited only by the ingenuity of chemists to devise new forms and the imagination of physicians and surgeons to employ them. Above all stands the felicitous fact that these substances are derived from native human proteins and all the errors and problems of foreign body reactions are at once resolved."

APPOINTMENT SOUGHT IN THE FIELD OF PATHOLOGY

A Fellow of the American College of Physicians who has had a distinguished career in the Medical Corps of the U. S. Army, now 62 years of age, seeks an appointment commensurate with his knowledge of pathology and experience. His credentials are: A.B. and M.D., Columbia University; postgraduate study at the Army Medical School and in Vienna, Austria, under Chiari and Erdheim; three years internship, New York Hospital; diplomate, American Board of Pathology; 36 years of active duty in the U. S. Army, including surgery, obstetrics, x-ray clinical laboratory procedures including bacteriology and serology, and during the past 20 years, gross and micro-pathology; teaching and lecturing; during World War I, in charge of Army Laboratory No. 1 in France; now in charge of a Service Command Laboratory, where duties include those of Chief of Pathological Section; member of numerous national medical societies, including the American College of Physicians; author of numerous publications in leading medical journals.

The Executive Secretary, Mr. E. R. Loveland, 4200 Pine St., Philadelphia 4, Pa., may be consulted concerning other qualifications of the candidate.

INTERNIST WANTED

A Fellow of the American College of Physicians, located in California, is desirous of obtaining an internist for association with him in practice. A doctor, under the age of forty, certified by the American Board of Internal Medicine, or eligible for certification, who would be interested in a connection first on a salary basis and later, if mutually agreeable, to form a partnership, is desired. Any interested physician should communicate with the Executive Secretary of the College, Mr. E. R. Loveland, 4200 Pine St., Philadelphia 4, Pa.

CORRECTION

In the June, 1946, issue of this journal, it was announced that Dr. William L. Howell, F.A.C.P., had retired from the Medical Corps, A.U.S., with rank of Major.

Dr. Howell was promoted to the rank of Lieutenant Colonel on June 1, 1945, and was recently (April 29, 1946) placed on inactive status. He is now engaged in the practice of internal medicine at 1801 Eye St., Northwest, Washington, D. C.

UNIVERSITY OF CALIFORNIA OFFERS REFRESHER COURSE

The University of California Extension Division and the Department of Psychiatry of the University's Medical School have announced a twelve weeks refresher course in psychiatry and neurology, which is to be given, under the direction of Dr. K. M. Bowman, Professor of Psychiatry, at the Langley Porter Clinic, San Francisco. Registration is limited to 60 doctors; preference will be first to graduates of the Medical School and to veteran physicians. Among the subjects to be covered are psychobiology, psychoses and psychoneuroses, clinical neurology, and electroencephalography. The fee for the course is \$200, payable in advance. Dr. Stacy R. Mettier, F.A.C.P., Head of Postgraduate Instruction, Medical Center, University of California, San Francisco 22, Calif., will receive applications for registration.

Dr. R. Manning Clarke, F.A.C.P., removed from Camden, N. J., toward the end of June to San Diego, Calif., where he has become the internist for the Sand-Oster Clinic.

Dr. Horace K. Richardson, F.A.C.P., Baltimore, was recently elected President of the Maryland Association of Private Practicing Psychiatrists.

ASSOCIATE INTERNIST WANTED

A Fellow of the American College of Physicians, located in Indiana, is desirous of obtaining an associate in the practice of Internal Medicine. He is a man widely known with a large practice. He wants an associate who is already certified by the American Board of Internal Medicine, or one who, at least, has the necessary background for certification; an extraordinarily good opportunity for some internist who is anxious to establish himself and who is willing to carry his part of the load. Any interested physician should communicate with the Executive Secretary of the College, Mr. E. R. Loveland, 4200 Pine Street, Philadelphia 4, Pa., making reference to "AO-2."

The War Department has announced the appointment of consultants in neuropsychiatry to the Secretary of War. The first consultant is to be Dr. William C. Menninger, F.A.C.P., Topeka, Kan.; other members of the College appointed as consultants are Dr. Lauren H. Smith, F.A.C.P., St. Louis, Mo.; Dr. Norman G. Brill (Associate), Silver Springs, Md.; Dr. John H. Greist (Associate), Indianapolis, Ind.; Drs. Clarke H. Barnacle, F.A.C.P., Edward G. Billings, F.A.C.P., and Franklin Ebaugh, F.A.C.P., all of Denver, Colo.

Brigadier General W. Lee Hart, U. S. A. (retired), F.A.C.P., has been honored by the award of the degree of Doctor of Humanistic Letters by the Southwestern Medical Foundation of Dallas, Tex.

Dr. Walter L. Bierring, F.A.C.P., Des Moines, has been appointed Professor Emeritus of Theory and Practice of Medicine in the State University of Iowa College of Medicine.

Dr. Albert D. Foster, F.A.C.P., Portland, Me., has been appointed health officer of that city.

Dr. Lewis J. Moorman, F.A.C.P., Oklahoma City, has received appointment as consultant to the Veterans Administration.

Dr. E. Sterling Nichol, F.A.C.P., Miami, Fla., has been elected president of the Florida chapter of the American College of Physicians.

Dr. Julius L. Wilson, F.A.C.P., and Dr. Maurice Campagna, F.A.C.P., New Orleans, were recently reelected President and Vice-President, respectively, of the Louisiana Tuberculosis Association.

On the occasion of the recent annual meeting of the Medical Society of the State of North Carolina, Dr. George E. Bell, F.A.C.P., Wilson, was elected First Vice-

President of the Society. Dr. James Bullitt, F.A.C.P., Chapel Hill, was elected Second Vice-President. Drs. W. C. Davison, F.A.C.P., Durham, and C. C. Carpenter, F.A.C.P., Winston-Salem, were elected to the Editorial Board of the North Carolina Medical Journal.

Dr. Dunne W. Kirby, F.A.C.P., formerly on the faculty of the Hahnemann Medical College and Hospital of Philadelphia, who served through the war in the Medical Corps of the Naval Reserve, has transferred to the Regular Navy with the rank of Commander, and is now stationed at the U. S. Naval Hospital, Newport, R. I.

Dr. Henry P. Close (Associate), Philadelphia, has retired from private practice and is now devoting his whole time to the Veterans Administration as Chief of the Medical Service, Coatesville Veterans Hospital, Coatesville, Pa.

The Kansas City Southwest Clinical Society will hold its 24th Annual Fall Clinical Conference, October 7-19, 1946. According to advanced announcements, the following members of the College will be guest speakers:

Charles A. Doan, M.D., F.A.C.P. (Internal Medicine, Research), Columbus, Ohio;
Tinsley R. Harrison, M.D., F.A.C.P. (Internal Medicine, Cardiology), Dallas, Tex.;
Walter L. Palmer, M.D., F.A.C.P. (Internal Medicine, Gastro-enterology), Chicago, Ill.

Dr. George W. Millett, F.A.C.P., formerly of San Francisco, has become Senior Medical Officer, Veterans Hospital, Montgomery, Ala.

Dr. Charles H. McEnerney, F.A.C.P., Washington, D. C., has been elected Third Vice-President of the Pan American Medical Association.

Dr. Felix J. Underwood, F.A.C.P., Jackson, Miss., executive officer of the Board of Health of the State of Mississippi, was a speaker at the dedication ceremonies of the North Mississippi Hospital.

Dr. Millard E. Winchester, F.A.C.P., Brunswick, Ga., has been elected President-elect of the Georgia Public Health Association.

Dr. Laurrie D. Sargent, F.A.C.P., presided at the Annual Meeting of the Tenth and Eleventh Councilor Districts of the Medical Society of the State of Pennsylvania, held at Washington, Pa., June 20. Dr. Walter F. Donaldson, F.A.C.P., Pittsburgh, presented 50-year testimonials to 15 members of the Society. Scientific papers were presented by Dr. Howard K. Petry, F.A.C.P., Harrisburg, and Dr. George J. Kastlin, F.A.C.P., Pittsburgh, Pa.

The Forty-Seventh Annual Meeting of the American Gastroenterological Association occurred May 24-25 at Atlantic City. Dr. A. H. Aaron, F.A.C.P., Buffalo, N. Y., delivered the presidential address and presented the Friedenwald Medal of 1946

to Dr. Frank H. Lahey and Dr. Sara Jordan, F.A.C.P., Boston. The following Fellows of the College presented papers at the sessions:

Dr. Mandred W. Comfort, Rochester, Minn., co-author, "Chronic Relapsing Pancreatitis."

Dr. Lester Dragstedt, Chicago, "The Role of Vagotomy in the Treatment of Peptic Ulcer."

Dr. Martin E. Rehfuss, Philadelphia, "Experimental Cholecystitis."

Drs. H. J. Moersch and B. R. Kirklin, Rochester, Minn., "Gastroscopy and Its Relationship to Roentgenology in the Diagnosis of Carcinoma of the Stomach."

Dr. Pedro L. Farinas Mayo, Havana, Cuba, co-author, "Postbulbar Duodenal Ulcers."

Dr. Martin G. Vorhaus, New York, "Hypertrophic Stenosis in the Adult."

Dr. Moses Paulson, Baltimore, co-author, "The Medical Management of Total Gastrectomy."

Drs. Henry A. Rafsky and Michael Weingarten (Associate), New York, "A Study of the Gastric Secretory Response in the Aged."

Dr. H. Marvin Pollard, Ann Arbor, "The Rate of Healing for Gastric and Duodenal Ulcers."

Dr. Lemuel G. McGee, Wilmington, Md., "Metabolic Disturbances in Workers Exposed to Dinitrotoluene."

Dr. J. A. Bargaen, Rochester, Minn., co-author, "Amino Acid Alimentation in Gastrointestinal Diseases."

Drs. Burrill B. Crohn, New York, and Milford O. Rouse, Dallas, co-authors, "Trauma in Relationship to the Perforation of Peptic Ulcer."

Dr. A. F. R. Andresen, Brooklyn, N. Y., "Traumatic Perforation of the Rectum and Sigmoid."

Dr. Walter L. Palmer, Chicago, "Giant Hypertrophic Gastritis."

Dr. Henry J. Tumen, Philadelphia, co-author, "Backache Due to Intra-abdominal Disease."

The eleventh annual convention of the National Gastroenterological Association was held in New York, June 19-21. Dr. Anthony Bassler, F.A.C.P., president of the association, was chairman of the program committee, of which Dr. Samuel Weiss, F.A.C.P., also was a member. Dr. Bassler, Dr. Clarence J. Tidmarsh, F.A.C.P., Montreal, vice-president of the association, and Dr. Henry A. Rafsky, F.A.C.P., New York, presided at sessions. Papers were presented by the following members of the college:

Dr. Zacharias Bercovitz, F.A.C.P., New York, "Parasitology and Tropical Medicine from a Military and Civilian Standpoint";

Dr. M. Herbert Barker, F.A.C.P., Chicago, "Acute and Chronic Gastrointestinal Manifestation of Infectious Hepatitis";

Dr. Sidney A. Portis, F.A.C.P., New York (co-author), "Changes in the Function of the Stomach with Varying Emotional Scales";

Dr. Martin E. Rehfuss, F.A.C.P., Philadelphia, "The Evolution of Chronic Cholecystitis";

Dr. William B. Rawls, F.A.C.P., New York, "Socialized Medicine";

Dr. Henry A. Monat, F.A.C.P., "Gastroscopy."

Dr. Bassler, Dr. J. Russell Twiss, F.A.C.P., and Dr. Burrill B. Crohn, F.A.C.P., all of New York, were discussors of the scientific papers.

Dr. Lathan A. Crandall, F.A.C.P., formerly of the University of Tennessee, has accepted appointment as Director of the Research Laboratories, Miles Laboratories, Inc., Elkhart, Ind.

Dr. Julius H. Comroe, Jr., F.A.C.P., Philadelphia, formerly Assistant Professor of Pharmacology in the University of Pennsylvania School of Medicine, has been appointed Professor of Physiology and Pharmacology in the University's Graduate School of Medicine. Dr. Comroe succeeds Dr. Edward Lodholz, who has been appointed Emeritus Professor of physiology.

Dr. Ross Moore, F.A.C.P., Los Angeles, delivered three lectures on the subject of "Diagnosis without Tools," constituting the recent sixth annual series of Lecture Conferences of Hollywood Presbyterian Hospital.

Dr. Reginald Fitz, F.A.C.P., Boston, delivered an address at the unveiling in San Francisco, July 4, of the portrait of Dr. Oliver Wendell Holmes. This portrait, painted by the noted artist Dean Cornwell and entitled "That Mothers Might Live," is the sixth in a series of "Pioneers of American Medicine" commissioned by Wyeth Incorporated.

Dr. Robert U. Patterson, F.A.C.P., Baltimore, retired June 30 from the deanship of the University of Maryland School of Medicine. Dr. Patterson, a former Surgeon General of the U. S. Army, retired from the Army with the rank of Major General to become dean of the University of Oklahoma School of Medicine. He began his deanship at the University of Maryland in 1942.

Dr. Edward A. Strecker, F.A.C.P., Philadelphia, delivered an address on "The Psychobiology of Psychiatric Research" at the dedication of the new Research Laboratory of the McLean Hospital, Waverley, Mass. The Laboratory will concern itself with investigation of mental disease problems and with the training of graduate students in methods of research in psychiatry.

Dr. Francis F. Borzell, F.A.C.P., is the recipient for 1945 of the Dr. Isidor P. Strittmatter Award. The award, consisting of a gold medal and scroll, was made by the Philadelphia County Medical Society for Dr. Borzell's "outstanding services in behalf of the contributions of organized medicine to World War II and his sincere devotion and constructive effort in safeguarding the principles of the American system of medicine."

Dr. Kendall Elsom, F.A.C.P., Philadelphia, Pa., has been appointed consultant in gastro-enterology to the Veterans Administration for the hospitals of the Third District, including Pennsylvania, New Jersey, and Delaware.

Dr. Henry R. Carstens, F.A.C.P., 2nd Vice President of the College, 1942-1944, has been appointed Medical Director of Branch Office No. 3 of the Veterans Administration. This office has charge of veterans' affairs in the Third District, which consists of Pennsylvania, New Jersey and Delaware. His headquarters are at Philadelphia.

A veteran of both World Wars, Dr. Carstens served in the last war as Colonel in the U. S. Army, and commanded the 17th General Hospital, Naples, Italy. Before the war, Dr. Carstens held positions as Associate Professor of Clinical Medicine, Wayne University College of Medicine, Chief of the Division of Internal Medicine, Outpatient Department, Harper Hospital, and chief of the Department of Medicine, Florence Crittenton Hospital, Detroit, Mich.

Dr. Henry LeRoy Bockus, F.A.C.P., Philadelphia, Pa., has been awarded the honorary degree of Doctor of Science by Dickinson College.

Dr. Edward B. Krumbhaar, F.A.C.P., Professor of Pathology in the University of Pennsylvania School of Medicine, has recently been elected to membership in the Harvard Board of Overseers.

Dr. John T. Farrell, Jr., F.A.C.P., Philadelphia, Pa., spoke on "The Rôle of Roentgenology in the Diagnosis and Management of Pyloric Obstruction," before the Dauphin (Pa.) County Medical Society, June 4.

It was recently announced that Dr. Edward Weiss, F.A.C.P., Philadelphia, Pa., had been elected President of the American Society for Research in Psychosomatic Problems.

Dr. Lester Hollander, F.A.C.P., Pittsburgh, Pa., is the author of a report, published recently in the Pennsylvania Medical Journal, on "Deodorants—Facts and Fallacies."

Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., recently addressed the Pennsylvania Dietetic Association on the subject, "Psychosomatic Medicine and Diet Therapy."

Dr. C. Howard Marcy, F.A.C.P., Pittsburgh, Pa., has retired from the presidency of the Pennsylvania Tuberculosis Society after a term of service of four years. Dr. John E. Fretz, F.A.C.P., Easton, Pa., has been elected first vice president of the Society; and Dr. T. Lyle Hazlett, F.A.C.P., Pittsburgh, Pa., and Dr. Elmer Highberger, F.A.C.P., Greensburg, Pa., have been elected to membership on its Board of Directors.

Colonel Allen Izard Josey, (MC), A.U.S., F.A.C.P., is the co-author of a recent paper in the Journal of the American Medical Association, entitled "Ruptured Inter-vertebral Disk Simulating Angina Pectoris."

Dr. David P. Barr, New York, President of the American College of Physicians, has been appointed a member of the newly organized Therapeutic Trials Committee of the American Medical Association. The purpose of this committee, which will function under the Council on Pharmacy and Chemistry, is to encourage sound evaluation of the clinical usefulness of new therapeutic agents. In this regard, the committee may assist pharmaceutical manufacturing firms in arranging clinical trials of new drugs. Other Fellows of the College who are members of the committee are

Dr. Chester S. Keefer, Boston; Dr. Walter W. Palmer, New York; Dr. W. Barry Wood, St. Louis; and Dr. Torald Sollmann, Cleveland.

A recent issue of the Journal of the American Medical Association contains an official statement by Dr. Cornelius P. Rhoads, F.A.C.P., New York, chairman of the Committee on Growth, National Research Council, on "Nitrogen Mustards in the Treatment of Neoplastic Disease."

Dr. Joseph M. Hayman, Jr., F.A.C.P., Cleveland, formerly Colonel in the Medical Corps, Army of the United States, has been awarded the Legion of Merit for outstanding service rendered by him while chief of medical service, Army Tropical Disease Center, Moore General Hospital, Swannanoa, N. C.

Dr. Thomas B. Magath, F.A.C.P., Rochester, Minn., formerly Commodore, Medical Corps, U. S. Naval Reserve, has been awarded the Legion of Merit for his studies and recommendations dealing with quarantine practices, concerning especially air traffic.

Dr. Albert M. Snell, F.A.C.P., Rochester, Minn., formerly Captain, Medical Corps, U. S. Naval Reserve, received commendation from the Secretary of the Navy for his "meritorious performance of duty as chief of the medical service, U. S. Naval Hospital, Oakland, Calif., March 20, 1944, to Nov. 5, 1945."

Dr. Samuel J. McClendon, F.A.C.P., San Diego, has become President of the California Medical Association. Dr. Dwight L. Wilbur, F.A.C.P., San Francisco, has been designated as the Editor of the journal of the association, California and Western Medicine.

The board of trustees of the newly organized American Allergy Fund includes Dr. Harry L. Alexander, F.A.C.P., St. Louis; Dr. J. Harvey Black, F.A.C.P., Dallas; Dr. Milton B. Cohen, F.A.C.P., Cleveland; Dr. Francis M. Rackemann, F.A.C.P., Boston and Dr. Oscar Swineford, Jr., F.A.C.P., Charlottesville, Va. The purpose of this organization is to promote the study and public understanding of allergy.

Dr. Oscar B. Hunter, F.A.C.P., Washington, D. C., has been appointed Adjunct Professor of Medicine in the Georgetown University School of Medicine.

Dr. John Favill, F.A.C.P., has been appointed head of neuropsychiatry at the Presbyterian Hospital, Chicago.

Dr. Abraham M. Balter, F.A.C.P., formerly of Aspinwall, Pa., has recently retired from military service in the Army with the rank of Lieutenant Colonel, after two and a half years' service, and is now on the staff of the Veterans Administration Hospital, Huntington, W. Va.

Dr. Nathaniel Uhr (Associate), formerly of New York City, has been retired from the Army with the rank of Colonel, after approximately four years' service, and has accepted an appointment at the Veterans Hospital, Topeka, Kan.

Dr. Olin B. Chamberlain, F.A.C.P., Charleston, S. C., has been elected president-elect of the South Carolina Medical Association.

At the annual meeting of the American College of Radiology, June 29, San Francisco, Dr. Edward H. Skinner, Kansas City, Mo., was elected president; Dr. Edwin C. Ernst, F.A.C.P., St. Louis, was elected vice-president.

Major General Norman T. Kirk, F.A.C.P., Surgeon General of the U. S. Army and Colonel Leon L. Gardner, F.A.C.P., Director of the Army Medical Library, have been granted honorary membership in the Brazilian Academy of Military Medicine.

Dr. Harold E. Himwich, F.A.C.P., Albany, New York, has accepted appointment as research physician, physician of clinical research branch of the Chemical Warfare Service, Edgewood Arsenal, Md. Dr. Himwich was formerly Professor of Physiology and Pharmacology in the Albany Medical College.

Dr. Thomas Parran, F.A.C.P., Surgeon General of the U. S. Public Health Service, served as chairman of the International Health Conference which took place in New York, N. Y., beginning June 20.

Dr. Maurice Fremont-Smith, F.A.C.P., Boston, was co-author of an article on "Cancer of Endometrium" recently published in the Journal of the American Medical Association.

Dr. Howard F. Root, F.A.C.P., Brookline, Mass., is a recent contributor to the Journal of the American Medical Association of a paper on "Allergy to Insulin."

It was announced recently that Major Gerald A. Beatty, F.A.C.P., Wilmington, Del., has been awarded the Bronze Star for his "energy, coöperative spirit, foresight and knowledge . . . exemplary devotion."

A portrait-medallion of Dr. Raymond B. Allen, F.A.C.P., has been presented to the President of the University of Illinois. Before his resignation from the University of Illinois to accept the presidency of the University of Washington, Dr. Allen had served as Executive Dean of the Chicago colleges and dean of the Medical School of the University of Illinois.

Drs. Morris M. Banowitch, F.A.C.P., and John B. D'Albora, F.A.C.P., Brooklyn, have received appointments as clinical professors in the department of medicine of the Long Island College of Medicine. Dr. Saverio C. Franco, F.A.C.P., has been appointed assistant clinical professor of medicine in the same medical school.

Dr. Joseph S. Hiatt, F.A.C.P., Sanatorium, N. C., has been appointed to the position of Superintendent of the Hugh Chatham Memorial Hospital in Elkin, N. C.

Dr. Edgar P. McNamee, F.A.C.P., Cleveland, has assumed the office of President of the Ohio State Medical Association.

Drs. Finley Gayle, Jr., F.A.C.P., Richmond, Va., and David C. Wilson, F.A.C.P., University, Va., participated in a neuropsychiatry seminar which was held at the Veterans Hospital, Roanoke, Va., in May.

At the recent annual meeting of the Association of American Physicians, Dr. O. H. Perry Pepper, formerly president of the American College of Physicians, was elected President of the Association. He succeeds as president Dr. Warfield T. Longcope, F.A.C.P. Also elected officers of the Association were Dr. Joseph T. Wearn, F.A.C.P., secretary, and Dr. Walter Bauer, F.A.C.P., Boston, treasurer.

Lt. Col. Joseph A. Resch, (MC), (Associate), has resigned his commission in the United States Army, effective September 14, 1946, and has received a fellowship in neurology at the University of Minnesota.

Dr. Anthony M. Kasich (Associate), Weehawken, N. J., addressed the American Association of the History of Medicine at Atlantic City, May 26, 1946, on the subject, "William Prout and the Discovery of Hydrochloric Acid in the Gastric Juices."

Col. Elias E. Cooley, F.A.C.P., has recently retired from the Medical Corps of the U. S. Army because of physical disability and is now residing at 12 Manly St., Greenville, S. C.

Dr. Joseph M. Hayman, Jr., F.A.C.P., Cleveland, has been appointed A.C.P. representative at the Fourth International Congress on Tropical Medicine and Malaria.

The 1947 Assembly of the Interstate Postgraduate Medical Association of North America, of which Dr. James E. Paullin, F.A.C.P., Atlanta, is president-elect, will be held in St. Louis, Mo., October 13-17, 1947.

A number of important appointments of members of the College to the faculty of the Medical College of Alabama, Birmingham, were among those recently announced by Dr. Roy R. Kracke, Dean. In the Department of Medicine, Dr. James S. McLester, F.A.C.P., has been made Professor and Chairman; Dr. Seale Harris, F.A.C.P., Professor emeritus; Dr. Edgar G. Givhan, Jr., F.A.C.P., Associate Professor; Dr. Joseph E. Hirsh, F.A.C.P., Associate Professor; Dr. James B. McLester, F.A.C.P., Associate Professor; Dr. James O. Finney, F.A.C.P., Assistant Professor; Dr. E. Dice Lineberry, F.A.C.P., and Governor for Alabama, Assistant Professor; Dr. R. Olney Russell, F.A.C.P., Assistant Professor; Dr. Ivan C. Berrey (Associate), Assistant Pro-

fessor. Dr. Tom D. Spies, F.A.C.P., has been appointed Visiting Professor of Research Medicine.

Dr. Claude C. McLean, F.A.C.P., received appointment in the Department of Pediatrics as Assistant Professor.

Dr. James J. Lightbody, F.A.C.P., Detroit, is Chairman of the Board of Trustees of the Wayne County Medical Society. Dr. Ralph A. Johnson (Associate), Detroit, is Editor of the Detroit Medical News.

The Twelfth Annual Meeting of the American College of Chest Physicians was held in San Francisco, June 27-30, 1946. Dr. J. Arthur Myers, F.A.C.P., Minneapolis, delivered the President's Address. Dr. James J. Waring, F.A.C.P., Denver, Colo., and Dr. Carl H. Gellenthien, F.A.C.P., Valmora, N. M., took part in a panel of medical experts.

A refresher course on Diseases of the Chest was a feature of the program. Among the participants in the course were Dr. R. H. Sundberg, F.A.C.P., San Diego, Calif., and Dr. Jacob J. Singer, F.A.C.P., Los Angeles, Calif.

Dr. Andrew L. Banyai, F.A.C.P., Milwaukee, Wis., served as co-chairman of the International Night Dinner program, at which Dr. William E. Ogden, F.A.C.P., Toronto, Ont., delivered a report. Dr. Banyai also presented a paper at the scientific sessions on "Inhalation of Carbon Dioxide for the Management of Cough." Dr. Frank N. Allan, F.A.C.P., Boston, Mass., was co-author of a paper on "Thymectomy in the Treatment of Myasthenia Gravis," and Dr. Alfred Goldman, F.A.C.P., San Francisco, Calif., reported on "The Surgical Treatment of Bronchial Adenoma."

Dr. H. Sheridan Baketel, F.A.C.P., of Greenland, N. H., received a certificate from the New Hampshire Medical Society at its 177th meeting last May in recognition of 50 years of continuous membership in that Society.

UNITED STATES PUBLIC HEALTH SERVICE MAKES GRANT FOR CANCER RESEARCH

A total of approximately \$50,000 in grants in aid to several American universities for cancer research has been approved by the U. S. Public Health Service Federal Grant Agency upon the recommendation of the National Advisory Cancer Council.

The University of Virginia will receive \$15,000 for a study of the fractionation of proteins of normal and cancerous tissues and of reactions to chemotherapeutic agents, and \$3,550 for work on the synthesis of compounds causing cancer cell damage.

George Washington University, Washington, D. C., received one grant of \$2,100 for a study of the effect of vitamin E on the growth and incidence of spontaneous and induced tumors in mice, and \$2,500 for a program of study of the toxicity, metabolism, physiological and pharmacological actions of substances that may be useful in destroying cancerous tissue or in halting its growth.

The University of Rochester, Rochester, N. Y., received \$10,000 for studies of gastric secretions in patients with cancer of the stomach.

Johns Hopkins University, Baltimore, Md., received \$7,700 for the study and control of enzymatic activity in relation to agents that interfere with the metabolism of normal and cancerous cells.

Loyola University, Chicago, Ill., received \$2,847 to support a study of the pathogenesis of experimental brain tumors.

Northwestern University, Chicago, Ill., received \$2,500 for the study of synthesis of hydrocarbons structurally related to the steroids.

The University of Minnesota, Minneapolis, Minn., received \$2,100 to support a study of gastritis in relation to carcinoma of the stomach.

Carson-Newman College, Jefferson City, Tenn., received \$700 to support work on the preparation of compounds for testing in the chemotherapy program on cancer.

RETIREMENTS FROM SERVICE

Since the last publication of this journal, the following members of the College have been reported retired or on terminal leave (to July 12, 1946 inclusive).

Theodore J. Abernathy, Washington, D. C. (Major, MC, AUS)

Glen I. Allen, Peoria, Ill. (Lt. Col., MC, AUS)

John S. Atwater, Rochester, Minn. (Lt., MC, USNR)

Abraham M. Balter, Aspinwall, Pa. (Lt. Col., MC, AUS)

Wayne C. Barnes, Springfield, Mass. (Major, MC, AUS)

Nathan J. Bender, Shreveport, La. (Lt., MC, USNR)

James L. Borland, Jacksonville, Fla. (Major, MC, AUS)

Lewis H. Bronstein, New York, N. Y. (Major, MC, AUS)

Frederic J. Burns, Pawtucket, R. I. (Lt. Comdr., MC, USNR)

M. Paul Byerly, Baltimore, Md. (Capt., MC, AUS)

Russell J. Callander, Tucson, Ariz. (Lt. Comdr., MC, USNR)

Julius Chasnoff, New York, N. Y. (Lt. Col., MC, AUS)

Samuel Cohen, Jersey City, N. J. (Capt., MC, AUS)

Frederick S. Coombs, Jr., Youngstown, Ohio (Lt. Col., MC, AUS)

Robert K. Dixon, Denver, Colo. (Lt. Col., MC, AUS)

Charles H. Drenckhahn, Champaign, Ill. (Lt. Col., MC, AUS)

Henry D. Ecker, New Orleans, La. (Surgeon, USPHS)

Henry Felson, Cincinnati, Ohio (Lt. Col., MC, AUS)

John F. Giering, Wilkes-Barre, Pa. (Lt. Col., MC, AUS)

William H. Gordon, San Francisco, Calif. (P. A. Surgeon, USPHS)

Meyer M. Harrison, Louisville, Ky. (Capt., MC, AUS)

R. Harold Jones, Fairmont, W. Va. (Col., MC, AUS)

Frank T. Joyce, Chickasha, Okla. (Capt., MC, AUS)

Newton A. Kilgore, Jr., Houston, Tex. (Lt. Col., MC, AUS)

Laurance W. Kinsell, East Stroudsburg, Pa. (Lt., MC, USNR)

Richard S. Knowlton, Cleveland, Ohio (Major, MC, AUS)

Alvin B. C. Knudson, Dwight, Ill. (Major, MC, AUS)

Herbert P. Lenton, Carlisle, Pa. (Capt., MC, AUS)

J. Elliot Levi, Baltimore, Md. (Capt., MC, AUS)

Robert M. Lintz, New York, N. Y. (Comdr., MC, USNR)
 Stephen L. Lirot, Meriden, Conn. (Lt., MC, USNR)
 Joseph Litwins, New York, N. Y. (Lt. Col., MC, AUS)
 Harold F. Machlan, Hines, Ill. (Col., MC, AUS)
 L. Martin Mares, Wenatchee, Wash. (Lt. Col., MC, AUS)
 Shaw McDaniel, Houston, Tex. (Comdr., MC, USNR)
 Milton Mendlowitz, New York, N. Y. (Major, MC, AUS)
 William C. Menninger, Topeka, Kan. (Brig. Gen., MC, AUS)
 William R. Minnich, Atlanta, Ga. (Capt., MC, AUS)
 Thomas C. Monaco, Boston, Mass. (Capt., MC, AUS)
 Raymond W. Monto, Detroit, Mich. (Major, MC, AUS)
 Sylvan E. Moolten, New York, N. Y. (Lt. Col., MC, AUS)
 Franklin D. Murphy, Philadelphia, Pa. (Capt., MC, AUS)
 Benjamin H. Neiman, Chicago, Ill. (Lt. Col., MC, AUS)
 James K. Norman, New Orleans, La. (Surgeon, USPHS (R))
 Howard M. Odel, Rochester, Minn. (Lt. Comdr., MC, USNR)
 J. Winthrop Pennock, Syracuse, N. Y. (Lt. Col., MC, AUS)
 William S. Randall, Jr., Pensacola, Fla. (Major, MC, AUS)
 Robert A. Reading, Cleveland, Ohio (Comdr., MC, USNR)
 Emmett L. Schield, Pomona, Calif. (Lt. Col., MC, AUS)
 Leo V. Schneider, Glenn Dale, Md. (Lt. Col., MC, AUS)
 Maurice A. Schnitker, Toledo, Ohio (Lt. Col., MC, AUS)
 John W. Shuman, Sr., Santa Monica, Calif. (Col., MC, AUS)
 Wilbur A. Smith, New York, N. Y. (Lt. Col., MC, AUS)
 Robert H. Talkov, Brookline, Mass. (Capt., MC, AUS)
 Nathaniel Uhr, New York, N. Y. (Lt. Col., MC, AUS)
 William G. Ure, Tucson, Ariz. (Capt., MC, AUS)
 Wesley Van Camp, Detroit, Mich. (Surgeon, USPHS (R))
 Robert C. West, Hamilton, Tex. (Lt. Col., MC, AUS)
 Paul L. White, Austin, Tex. (Lt. Col., MC, AUS)

It is intended to publish in book form a collection of subjective case histories written by physicians.

Such reports should cover a much broader field than that which is customarily called symptoms. The term "symptoms" is used to mean the total subjective experience of the patient caused by disease. To the commonly acknowledged symptoms, such as pain, fatigue, nausea, etc., must be added such subjective experiences as are related to the mental, emotional and economic aspects. Any subjective experience proceeds not in a theoretical vacuum of the "normal" or "average" person, but within the canvass of an established personality with all the modalities of intellect, emotions,

faith, codes of behavior, social and economic realities. The argument may then well be encompassed in two main questions:

1. How has my personality (in the fullest sense of the word) modified the disease? and
2. How has the disease modified my personality?

The writer believes that much more specifically directed work is urgently needed. He believes that one particularly fertile approach to this problem is to induce physicians to analyze and describe their own experiences with diseases they have or have had.

It would seem that the combination of objective medical knowledge with the subjective experience might be particularly fruitful of original contributions in this field.

In such a collection, emphasis should be placed on chronic or recurrent diseases, because they are likely to show, more than the acute ones, modifications caused by the patient's individuality, and more of such significant marks that diseases may leave on the individual in his mental, emotional, physical, social and professional life.

Each contributor should be limited by no other concern but the general aim of the collection. It is, therefore, expected that objective clinical details be limited to that minimum that is germane to the story. Full emphasis should be given to subjective symptoms, especially to those that the usual textbooks consider unessential or fail to mention. Considerable details are expected in the matter of psychological attitude to the disease as such, to pain, to the prognosis—right or wrong—to the limitations imposed by the disease or its consequences, to accomplished or attempted readjustments, and to peculiarities of the premorbid personality if it is essential to the total picture.

In many discussions that the writer has had while this plan slowly matured, the main and first objection raised was the impossibility of getting "unbiased accounts." This is simply met by the answer that unbiased accounts are neither expected nor desired, since it is precisely the individual experience that should be told.

Each contributor will have the choice whether or not he wishes to remain anonymous; and, if anonymity is desired, it will be strictly maintained.

Physicians, who may be interested to contribute reports of their illnesses, are invited to write to

MAX PINNER, M.D., *Editor*
AMERICAN REVIEW OF TUBERCULOSIS
463 Vermont Avenue
Berkeley 7, California

SPECIAL NOTICE

The Department of Medicine of the New York Post-Graduate Medical School and Hospital has available, for September 1, 1946, a Research Assistantship in Medicine. This project is a detailed clinical investigation of the ageing process in its various phases. Stipend to begin at \$2400 yearly in proportion to qualifications of candidate.

Requirements include graduation from a Grade A medical school in this country and several years training in an approved hospital, preferably a residency in medicine.

Inquiries and applications should be addressed to the Department of Medicine, New York Post-Graduate Medical School and Hospital, 301 East 20th Street, New York 3, New York.

READING LISTS AND BIBLIOGRAPHIES

By direction of the Board of Regents the Advisory Committee on Postgraduate Courses of the College attempts to obtain reading lists for each postgraduate course for publication in this journal, making these lists available to the entire membership of the College, in addition to better preparing the men who will take the courses. These lists are not to be considered all inclusive.

ALLERGY

Textbooks

- Allergy Theory and Practice. Robert A. Cooke. W. B. Saunders Co., Philadelphia, 1946 (in press).
 Allergy in Practice. S. M. Feinberg. Year Book Publishers, Chicago, 1944.
 Clinical Allergy. Louis Tuft. W. B. Saunders Co., Philadelphia, 1937.
 Dermatologic Allergy. M. B. Sulzberger. Charles C. Thomas Co., Baltimore, 1940.
 Occupational Diseases of the Skin. Louis Schwartz and Louis Tulipan. Lea and Febiger, Philadelphia, 1939.
 The Fundamentals of Immunology. W. C. Boyd. Interscience Publishing Co., New York, 1943.
 The Specificity of Serological Reactions. Karl Landsteiner. Harvard University Press, Cambridge, Mass., 1945.
 Hay Fever Plants. R. P. Wodehouse. Chronica Botanic Co., Waltham, Mass., 1945.

Monographs

- Allergy. C. E. Von Pirquet. Archives of Internal Medicine 7: 259, 1911.
 Anaphylaxis. Hypersensitiveness and Allergy. W. W. C. Topley. An Outline of Immunity, Chapter 12, p. 192. Wm. Wood Co., 1935.
 Diseases of Allergy. Robert A. Cooke. P. 1156, Internal Medicine. John H. Musser. Lea and Febiger, Philadelphia, 1945, fourth edition.
 Diseases of Allergy; Introduction and Hay Fever. Robert A. Cooke. Page 467, A Textbook of Medicine. Russell L. Cecil. W. B. Saunders Co., Philadelphia, 1943, sixth edition.
 Human Sensitization. Robert A. Cooke and A. Vander Veer. Journal of Immunology 1: 201, 1916.
 Herter Lectures. H. H. Dale. Bulletin Johns Hopkins Hospital 31: pp. 257, 310, 373, 1920.
 Anaphylaxis. Carl A. Dragstedt. Physiol. Rev. 21: 563, 1941.
 Histamine and Anaphylaxis. W. Feldberg. Annual Review of Physiology, March, 1941.
 Serum Sickness and Analogous Reactions from Certain Drugs—Particularly the Sulfonamides. W. T. Longcope. Medicine, 22: 351, 1943.
 War Department Technical Bulletin. T. B. Med., 202. War Department, Washington D. C., October 15, 1945.

*Articles**Immunological Basis of Sensitization*

- Horse Asthma Following Blood Transfusion. M. A. Ramirez. J. A. M. A. 73: 984, 1919.
 Studies on the Reactions of Asthmatics and on Passive Transference of Hypersusceptibility. Arent de Besche. Am. J. Med. Sciences 166: 265, 1923.
 Indirect Method of Testing. M. Walzer. J. Allergy 1: 231, 1930.

- Studies in Hypersensitiveness. XXXVI. A Comparative Study of Antibodies Occurring in Anaphylaxis, Serum Disease and the Naturally Sensitive Man. Robert A. Cooke and W. C. Spain. *J. Immunol.* 17: 295, 1929.
- Passive Sensitization of Human Skin by Serum of Experimentally Sensitized Animals. W. B. Sherman, A. Stull and S. F. Hampton. *J. Immunology* 36: 447, 1939.
- Serological Evidence of Immunity with Co-existing Sensitization in a Type of Human Allergy. Hay Fever. R. A. Cooke, J. H. Barnard, S. Hebal and A. Stull. *J. Exper. Med.* 62: 773, 1935.
- Immunological Studies of Pollinosis. I. The Presence of Two Antibodies Related to the Same Pollen Antigen in the Serum of Treated Hay Fever Patients. M. H. Loveless. *J. Immunol.* 38: 25, 1940.
- Studies in the Transmission of Sensitization from Mother to Child in Human Beings. S. D. Bell and Z. Eriksson. *J. Immunol.* 20: 447, 1931.
- The Placental Transmission of Antibodies in the Skin-Sensitive Type of Human Allergy. W. B. Sherman, S. F. Hampton and R. A. Cooke. *J. Exper. Med.* 72: 611, 1940.
- The Question of the Elimination of Foreign Protein (Eggwhite) in Woman's Milk. H. H. Donnally. *J. Immunol.* 19: 15, 1930.
- The Production in the Rabbit of Hypersensitive Reactions to Lens, Rabbit Muscle and Low Ragweed Extracts by the Action of Staphylococcus Toxin. E. L. Burky. *J. Allergy* 5: 466, 1934.

General Clinical Allergy

- History Taking in Allergy: An Outline for, and a Comparison of Results from 200 Histories and Skin Tests. O. Swineford, Jr. and W. M. Weaver. *Ann. Int. Med.*, 20: 293, 1944.
- Studies in Specific Hypersensitiveness. III. On Constitutional Reactions: The Dangers of the Diagnostic Cutaneous Test and Therapeutic Injection of Allergens. R. A. Cooke. *J. Immunol.* 7: 119, 1922.
- The Occurrence of Constitutional Reactions in the Treatment of Hay Fever and Asthma: Analysis of the Causative Factors. F. F. Furstenberg and L. N. Gay. *Bull. Johns Hopkins Hospital* 60: 412, 1937.
- Treatment of Allergic Disorders with Histamine and Histaminase. H. L. Alexander. *J. Lab. & Clin. Med.* 26: 110, 1940.

Asthma

- Asthma in Children. R. A. Cooke. *J. A. M. A.* 102: 664, 1934.
- Infective Asthma. Indication of Its Allergic Nature. R. A. Cooke. *Am. J. Med. Sci.* 183: 309, 1932.
- The Pathology of Bronchial Asthma. H. L. Huber and K. K. Koessler. *Arch. Int. Med.* 30: 689, 1922.
- Effects on Heart of Long Standing Bronchial Asthma. H. L. Alexander, D. Luten and W. B. Kountz. *J. A. M. A.* 88: 882, 1927.
- Studies in Specific Hypersensitiveness. IV. New Etiologic Factors in Bronchial Asthma. R. A. Cooke. *J. Immunol.* 7: 147, 1922.

Nasal Allergies

- Seasonal Hay Fever and Asthma Due to Molds. S. M. Feinberg. *J. A. M. A.* 107: 1861, 1936.
- Importance of Allergy in Etiology and Treatment of Nasal Mucous Polyps. R. A. Kern. *J. A. M. A.* 103: 1293, 1934.
- The Preparation and Standardization of Pollen Extracts for the Treatment of Hay Fever. R. A. Cooke and A. Stull. *J. Allergy* 4: 87, 1933.

- The Relative Merits of Seasonal and Perennial Treatment of Hay Fever. A. Vander Veer. J. Allergy 7: 578, 1936.
- Calculating Pollen Concentration of the Air. E. C. Cocke. J. Allergy 8: 601, 1937.
- Evaluation of the Ragweed Hay Fever Resort Areas of North America. O. C. Durham. J. Allergy 8: 175, 1937.
- Moisture Characteristics of Pollen. A. B. Berresford and Robert A. Cooke. J. Allergy 16: 87, 1945.
- A Method of Determining the Probability of Constitutional Reactions During Treatment of the Ragweed Hay Fever Patient. W. B. Sherman and S. Heballd. Am. J. M. Sc. 203: 383, 1942.

Immunological Basis of Sensitization

- Immunological Studies of Pollinosis II. Passive Sensitization of Man Through Transfusion. Mary H. Loveless. J. Immunol. 41: 15, 1941.
- The Cellular Transfer of Cutaneous Hypersensitivity to Tuberculin. Merrill W. Chase. Proc. Soc. Exper. Biol. & Med. 59: 134, 1945.

Asthma

- Deaths from Asthma. F. M. Rackemann. J. Allergy 15: 245, 1944.
- Molds in Relation to Asthma and Vasomotor Rhinitis. A Review. M. B. Morrow and E. P. Lowe. Mycologia 35: 638, 1943.
- The Importance of Chronic Sinusitis in the Treatment of Bronchial Asthma R. C. Grove. New York State J. Med. 41: 455, 1941.
- Treatment of Asthma and Hay Fever. Robert A. Cooke. New York State J. Med. 43: 17, 1943.

Allergy of the Digestive System

- Allergy of the Abdominal Organs. M. Walzer. J. Lab. & Clin. Med. 26: 1867, 1941.
- Gastro-intestinal Manifestations of Allergy. R. A. Cooke. Bull. N. Y. Acad. Med. Second Series IX: 15, 1933.
- Food Idiosyncrasy as a Factor of Importance in Gastro-enterology and in Allergy. W. T. Vaughan. Rev. Gastroenterol. 5: 1, 1938.

Allergic Dermatoses

- The Treatment of Infantile Eczema from the Point of View of the Pediatrician. L. W. Hill. J. A. M. A. 111: 2113, 1938.
- A Consideration of Some Allergy Problems. I. Allergic Dermatitis (Eczema). Robert A. Cooke. J. Allergy 15: 203, 1944.
- A Tentative Classification of Allergic Dermatoses. M. B. Sulzberger, F. Wise and J. Wolf. J. A. M. A. 104: 1489, 1935.
- A Critical Review of 170 Cases of Urticaria and Angioneurotic Edema Followed for a Period of from Two to Ten Years. A. I. Fink and L. N. Gay. J. Allergy 5: 615, 1934.
- Report of the Investigation and Successful Treatment (Preventive) of Dermatitis Resulting from the Handling of Tulip Bulbs. A. H. W. Caulfeild. J. Allergy 8: 181, 1937.

Miscellaneous Allergy

- The Role of Hypersensitivity in Periarteritis Nodosa as Indicated by Seven Cases Developing during Serum Sickness and Sulfonamide Therapy. A. R. Rich. Bull. Johns Hopkins Hosp. 71: 123, 1942.
- Transient Focal Pulmonary Edema. C. B. Peirce, E. F. Crutchlow, A. T. Henderson and J. W. McKay. Am. Rev. Tuberc. 52: 1, 1945.

- Henoch's Purpura Based on Food Allergy. S. F. Hampton. J. Allergy 12: 579, 1941.
- Principles and Practices of Inhalational Therapy. Alvan L. Barach. J. B. Lippincott Co., Philadelphia, 1944.
- Cerebral Symptoms Induced by Angioneurotic Edema. F. Kennedy. Arch. Neurol. and Psychiat. 15: 28, 1926.
- Allergic Migraine. W. T. Vaughan. J. A. M. A. 88: 1983, 1927.
- Food Allergy in Henoch's Purpura. H. L. Alexander and C. H. Eyermann. Arch. Dermat. & Syph. 16: 332, 1927.
- Allergy Induced by Immunization with Tetanus Toxoid. R. A. Cooke, S. F. Hampton, W. B. Sherman and A. Stull. J. A. M. A. 114: 1854, 1940.
- Physical Allergy. W. W. Duke. J. A. M. A. 84: 736, 1925.
- Allergy in Drug Idiosyncrasy. R. A. Cooke. J. A. M. A. 73: 759, 1919.

OBITUARIES

DR. EMANUEL LIBMAN

Dr. Emanuel Libman died in Mt. Sinai Hospital on June 28, 1946, at the age of seventy-three. Dr. Libman was born August 22, 1872, in New York City; attended the College of the City of New York and received his medical degree from Columbia University College of Physicians and Surgeons, 1894. For many years Professor of Clinical Medicine at his Alma Mater; consulting physician, Mt. Sinai, Montefiore, Harlem, Beth Israel, French, Methodist (Brooklyn), Bronx, Israel-Zion (Brooklyn), and Beth-El (Brooklyn) Hospitals, and Hospital for Deformities; author of numerous publications; former President, New York Pathological Society; Member, New York Academy of Medicine, American Society of Clinical Investigation, Harvey Society, American Association of Immunologists, Association of American Physicians, and many others; Diplomate, American Board of Internal Medicine; Fellow, American College of Physicians since 1928.

Dr. Libman was a very famous internist, a stimulating teacher and possessed a keen mind for research, and his loss to the medical profession will be very keenly felt.

ASA L. LINCOLN, M.D., F.A.C.P.,
Governor for Eastern New York

DR. MORTIMER COHEN

Dr. Mortimer Cohen, F.A.C.P., of Pittsburgh, Pennsylvania, died suddenly on June 20, 1946, at the age of 49 years. Dr. Cohen received his public school and high school education in the schools of the City of Pittsburgh. He received both his college and medical school education at the University of Pittsburgh, graduating from the School of Medicine in 1921. He served his internship at Passavant Hospital, Pittsburgh, after which he became associated with The Elizabeth Steel Magee Hospital and the Department of Pathology, University of Pittsburgh. This association was on a full time basis, beginning the latter part of 1922 and continuing until the time of his death. His work in connection with the Hospital and the School was confined to the field of Pathology. He became Associate Professor of Pathology in 1928. As a teacher of Pathology and as a Pathologist to the Hospital, his work was of the highest quality. As a consultant in Pathology his judgment and advice will be greatly missed by his associates. He was a Diplomate of the American Board of Pathology, a Fellow of the American College of Physicians (1932), a Fellow of the American Medical Association, and a member of The Pennsylvania Medical Society, Allegheny County Medical Society, The Association of Pathologists and Bacteriologists, The American Society of Clinical Pathologists, International Association of Medical Museums, The Clinical Pathological Society of Pittsburgh, Society of Biological Research, Sigma Xi and Alpha Omega Alpha.

Dr. Cohen's untiring devotion to his work was always an inspiration to his associates; especially was this true during the trying years of World War II.

On the evening of June 20 while working in his laboratory at the Hospital he suffered an attack of coronary thrombosis from which he died a few hours later.

His passing is a distinct loss to the medical profession.

GEORGE R. LACY, M.D., F.A.C.P.

COLONEL WALTER STEEN JENSEN

Colonel Walter Steen Jensen, M.C., died in Washington, D. C., on April 3, 1946.

An outstanding medical officer who was exceptionally well-liked by his fellow officers, he was commissioned October 29, 1925. At the time of his death Colonel Jensen was on duty in the Office of The Air Inspector, Headquarters, Army Air Forces. His death came as a shock to his many close friends who knew and loved him.

Born the son of Danish immigrant parents on August 11, 1894, in Brooklyn, N. Y., the late Colonel Jensen served overseas as an enlisted man in World War I. While in action with the 151st Field Artillery, 42nd Division (Rainbow Division), he was awarded the Purple Heart and an Oak Leaf Cluster for meritorious service, in addition to many campaign ribbons.

Early in World War II, Colonel Jensen was a member of the pioneer American mission which flew from Alaska to Moscow. In 51 days during which he studied Russian technics of aviation medicine, Colonel Jensen's observations resulted in important medical information to the United States Army. He was awarded the Legion of Merit for his work in connection with that mission. For security reasons, the medal was not awarded him until 1945.

From then on Colonel Jensen specialized in aviation medicine and was named Deputy Air Surgeon the same year. Later he served as Air Surgeon for the Pacific Theater before moving up into battle zones on the staff of Lieutenant General Barney Giles.

Upon his return from the Pacific early this year, the deceased Army officer was assigned temporarily to the Office of the Air Surgeon.

An accomplished administrator, Colonel Jensen served as executive officer in the Army and Navy General Hospital, Hot Springs, Ark., commencing in 1937. When war broke out he was Medical Director, Newfoundland Base Command, and served as liaison officer between the U. S. Army and Newfoundland health authorities.

An aviation enthusiast, Colonel Jensen attended the School of Aviation Medicine, Randolph Field, Texas, where he taught on the faculty and also served as Director of Neuropsychiatry at the school. Prior to that he was Chief, Neuropsychiatric Section, Gorgas Hospital, Panama. He also took

postgraduate work at Army Medical Center, Walter Reed General Hospital, Washington, as far back as 1928.

Upon his discharge from the Army following World War I, Colonel Jensen completed his college studies and graduated from Union College, Lincoln, Neb., with an A.B. degree in 1920. Four years later he received his M.D. degree from College of Medical Evangelists, Los Angeles, Calif. He completed his internship at White Memorial Hospital, California. He was commissioned a First Lieutenant, Medical Corps, on October 29, 1925.

The deceased was a Fellow in The American College of Physicians. He held membership in American Medical Association, American Psychiatric Association, and Association of Military Surgeons of the United States. He was author of several published articles and "Outline of Neuropsychiatry."

Major General NORMAN T. KIRK, M.D., F.A.C.P.,
Governor for the Medical Corps, U. S. ARMY.

DR. FRANCIS L. BARTHELME

Dr. Francis Lorraine Barthelme, B.S., M.D. (Associate), Effingham, Ill., died in St. Anthony's Hospital on March 8, 1946. He was 49 years old. Dr. Barthelme was graduated from the St. Louis University School of Medicine in 1923. He was attending Physician at St. Anthony's Hospital for a number of years and was formerly a member of the staff of the Evangelical Deaconess Hospital of St. Louis; elected an Associate of the College in 1928, before limitation was placed on the maximum Associate term; entered the medical corps of the Army of the United States on September 22, 1942 as Captain; service was terminated in November, 1943.

Dr. Barthelme is survived by his wife and three children.

DR. ALBERT SOILAND

Albert Soiland, M.D., D.M.R.E., F.A.C.P., internationally known radiologist of Los Angeles, California, died of a heart attack on May 14, 1946, while visiting at Stavanger, Norway.

Dr. Soiland was born at Stavanger on May 5, 1873. When a small boy he came to the United States. Later he attended the University of Illinois and in 1900 received his M.D. degree from the University of Southern California School of Medicine. He later became professor of radiology at this institution.

Dr. Soiland became interested in roentgenology and the treatment of cancer before he had graduated in medicine. He established the first x-ray office in Southern California. He founded, and was the Past President of the American College of Radiology; Past President, Radiological Society of North America; Past President, American Radium Society; Founder and Past Chairman, Section of Radiology, American Medical Association; Member, American Society for the Control of Cancer; Fellow (Honorary), Northern Society for Medical Radiology (Scandinavia); Member, Board of

Trustees, Pan American Medical Association; Member of the American Roentgenology Society; Diplomate of American Board of Radiology. He had been a Fellow of the American College of Physicians since 1917. Dr. Soiland was the author of numerous publications, and had studied in most of the important cancer clinics throughout the world.

He was prominently associated with yachting on the Pacific Coast and had organized, and was the first commodore of the Newport Harbor Yacht Club in 1914. He also was commodore of the Pacific Coast Yacht Association, and was instrumental in establishing the Trans-Pacific Yacht races of Hawaii, taking part in three of these and winning one.

He served in World Wars I and II and rose to the rank of Captain in the U.S. Naval Reserve and was said to be the oldest Captain on active duty.

Some time before his death, he created the Albert Soiland Cancer Foundation. This is a non-profit corporation which will ultimately control all of the property owned by Dr. Soiland and his widow, Mrs. Dagfine B. Soiland. This research foundation will endow fellowships in cancer research.

Dr. Soiland was a Mason and a member of many local clubs and organizations. Phi Rho Sigma and Theta Nu Epsilon were his fraternities.

The American College of Physicians has lost one of its most distinguished members.

LELAND HAWKINS, M.D., F.A.C.P.

Governor for Southern California

DR. I. HARRIS LEVY

Dr. I. Harris Levy, F.A.C.P., age 77 years, died in his sleep on July 9, 1946.

Dr. Levy was one of the first physicians in Syracuse to use the stomach tube in diagnosis. He also was one of the first to use roentgen-ray studies of the gastrointestinal tract. He was considered an authority on gastrointestinal disease and was highly respected in Central, Northern and Southern New York State. He had a large private and consulting practice.

Dr. Levy was an ardent student and a very keen clinician. For many years he was attending physician at the University Hospital. During his service he had the privilege of seeing many cases of typhoid fever and it was the privilege of the writer to work with him at that time. Dr. Levy's service at that time was the first to use the Coleman-Shattuck diet for the treatment of typhoid fever.

Dr. Levy traveled extensively and studied many times in Europe at the clinics in Berlin and Vienna. His hobbies were golf and archeology.

He was a diplomate of the American Board of Internal Medicine; a member of the American Gastro-Enterological Society, the New York State Medical Society, the Syracuse Academy of Medicine and the Practitioners' Club. He was also a member of Phi Beta Kappa and Alpha Omega Alpha.

honorary scholastic societies. He had been a Fellow of the American College of Physicians since 1916, almost from the inception of the College. He taught in the Syracuse University College of Medicine for over fifty years. He retired from the professorship of Medicine in 1931, since which time, until the time of his death, he was professor emeritus.

Dr. Levy was very highly respected for his learning and his scholastic attainments. He was a very skillful physician. He had many friends throughout the country. His death will be mourned by many and his loss to the medical profession will be keenly felt.

EDWARD C. REIFENSTEIN, M.D., F.A.C.P.,
Governor for Western New York

CAPTAIN EARL CURTIS CARR

Captain Earl Curtis Carr, (MC), USN, died on May 9, 1946, at the Naval Hospital, Philadelphia, Pennsylvania. Until a short time before his admission to the Naval Hospital, Philadelphia, he had been Medical Officer in Command of the Naval Hospital, Norman, Oklahoma. Captain Carr was born June 13, 1892, at Fulton, Illinois. He graduated from the Medical School, University of Illinois, with the degree Doctor of Medicine in 1915, and served an internship at St. Louis City Hospital, 1915-1916, and as resident physician in the Louisville City Hospital. He entered the Naval Medical Reserve Corps in 1916. He was commissioned in the Medical Corps, U. S. Navy, June 5, 1917.

His service in the Navy included duty at the Naval Air Station, Pensacola, Navy Yards at New York and Philadelphia, Naval Training Station, Great Lakes, Illinois, and the Bureau of Medicine and Surgery. During World War I he served on the USS St. Louis from June 1917 to October 1919. He completed a postgraduate course at the Naval Medical School and a postgraduate course in internal medicine. He was a Fellow of the American College of Physicians, the American College of Chest Physicians, and the Association of Military Surgeons of the United States. Captain Carr is survived by his wife and a son, William. Mrs. Carr is a sister of Commander W. B. Hetfield, (MC), USN, (Ret.). Captain Carr also had a brother in the Medical Corps of the Navy, Captain Claude W. Carr.

Funeral services and burial were on May 13 in Arlington National Cemetery.

ROSS T. MCINTIRE, Vice Admiral, Medical Corps,
Surgeon General, U. S. Navy,
Governor, American College of Physicians

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EVALUATION OF THE SEVERAL METHODS FOR TREATING GRAVES' DISEASE AVAILABLE TODAY *

By J. H. MEANS, M.D., F.A.C.P., *Boston, Massachusetts*

THE proof of the pudding is the eating, and similarly the proof of the treatment of any disease lies in the practice thereof, and that for a sufficient length of time and under adequately controlled circumstances. Forms of therapy ultimately survive or disappear in accordance with the impression they make on dispassionate, yet qualified observers. Time is a requisite in their appraisal.

The inventors of new remedies may often be classified as qualified, but not always as dispassionate. Since they are human, like the rest of us, complete objectivity with regard to their inventions is perhaps more than we have a right to expect of them.

I have been concerned with the appraisal of methods available for treating Graves' disease for most of my professional life. Since I am the inventor of none of them, I may lay claim to some objectivity in their evaluation.

The doctor, of course, should treat not only the disease but also the patient. Sometimes it is more important to treat the patient than his disease, but not so in the case of Graves' disease. In my somewhat long contact with this malady it has been my experience that except in rare instances, if you cure the disease you cure the patient. What I mean to say is that, although Graves' disease may be precipitated by shocking experiences, the imbalance which I believe the malady to be persists long after the provoking factor has gone, and the cure is to be found in the restoration to normal function of systems of the body whose derangement has outlasted what caused it. When the question has been: "Has this patient a psychoneurosis in addition to his Graves' disease?" our experience has been that usually when the thyrotoxicosis has been controlled the evidence of psychoneurosis disappears. There-

* Read at the Philadelphia meeting of the American College of Physicians.
From the Thyroid Clinic, Massachusetts General Hospital.

fore, I would say that in patients with Graves' disease, the doctor's chief job is to treat the disease.

What methods have we for doing this? In the past many drugs, iron, arsenic, digitalis, iodine, ergot, hydrocyanic acid, quinine, thyroid, and others have been tried in the treatment of Graves'; also other forms of treatment, such as prolonged rest, electricity, hydrotherapy, anti-sera, etc., have been used. None of these measures was of any great significance save iodine, and that had fallen into desuetude following Kocher¹ because of his pronouncements against it, until the late H. S. Plummer² reintroduced it in 1923.

The more modern methods of treatment which I wish now to appraise are as follows:

1. Subtotal ablation of the thyroid.
2. Antithyroid drugs.
3. Irradiation of the thyroid by means of radioactive iodine.

These various measures are used with the purpose of reducing thyrotoxicosis. There is another category of therapies which are designed to relieve the ophthalmic involvement when that is the more serious part of the picture. I have discussed these latter in a recent paper³ and will not consider them further today.

The measures I have mentioned which are aimed at the thyrotoxicosis are sometimes used in combination. Thus surgical removal of the thyroid presupposes adequate preparation for operation, which nowadays, except in very mild cases where iodine alone may suffice, should include, unless a contra-indication be encountered, the use of thiouracil or one of its relatives, and iodine. It is very important in appraising thyroid surgery to consider not only progress in operative technic and in anesthesia, but also in the specific preparation of the patient for operation.

I said in the beginning that the proof of a treatment is to be found in the practice of it. So now let me tell you that no longer than four years ago I attempted to identify the best treatment available for Graves' disease by surveying the ways in which we actually had treated it during a 25 year period.⁴ I may say further that at that time I reached conclusions rather different from those I shall draw today, and those that I shall draw today are probably different from those that others may draw today or that I may draw tomorrow. The fact is that there are different schools of thought on this subject. When a therapy is introduced which converts a previously fatal disease into one completely relievable, like insulin in diabetes or liver in pernicious anemia, there are no different schools of thought as to how to treat the disease, except in the matter of details.

But this is not the situation in Graves' disease. In the first place, Graves' disease is not necessarily fatal. Even in the absence of all treatment, spontaneous recovery is quite possible. In the second place, we already had,

prior to the introduction of the latest forms of therapy, methods of treatment which on the whole were fairly satisfactory. Our problem, therefore, is to determine, if possible, which of *several* effective forms of treatment now available actually offers the patient the greatest chance of complete and lasting relief, and which subjects him to the least possible risk, inconvenience and expense. We also should discover whether in a certain type of case one method of treatment is preferable, while in another type of case a different method of treatment is to be preferred. Since Graves' disease may run a chronic course with spontaneous remissions and relapses, such an evaluation of methods of treatment is far from simple.

In my paper entitled "How We Have Treated Graves' Disease during a Quarter Century" published four years ago,⁴ I pointed out that on the basis of that experience the conclusion seemed warranted that subtotal thyroidectomy following adequate preparation by a course of iodine offered more overall benefit than any other program then available. I pointed out also that in certain cases long continued exhibition of iodine alone had been found to be sufficient treatment. This last may still hold true occasionally.

At the onset of our studies in 1914, Aub and I⁵ decided to test the relative merits of roentgen-ray treatment and surgery for Graves' disease. That was in the era before the routine use of iodine, and surgical mortality was rather appalling. For that reason non-surgical methods of therapy found much favor. I cannot go into the details now of how we compared roentgen therapy and surgical; it has all been published,^{5, 6} but I may recall that our overall conclusions were that irradiation of the thyroid by roentgen-ray brought about an apparent cure in approximately one-third of the cases, benefit in another third, and no benefit in the remaining third. For a time, therefore, it was usual to use roentgen-ray treatment first, with the hope that it might be all that was needed, but operating later in most cases in which it failed.

In 1923, with the introduction of iodine and consequent decrease in operative mortality, subtotal thyroidectomy after preparation with iodine became the method of choice. Now in 1946, with newer forms of therapy available, the whole question of what is the best form of treatment for Graves' disease is again thrown wide open.

Before approaching this question directly, let us consider for a moment what contribution the newer methods may have made when used in conjunction with surgery. If one compares the preparation of the patient for operation by the administration of an antithyroid drug, such as thiouracil, with the older one of iodine alone, then it can be said that by thiouracil it is possible to deliver the patient to the surgeon more dependably in a euthyroid state than was ever possible by iodine.⁷ But the use of thiouracil alone, all agree, gives the surgeon a very vascular gland in which hemostasis is difficult. However, it is also evident that by giving both thiouracil and iodine together,^{8, 9} one can achieve the nearly perfect preparation. Not only is the

patient in a euthyroid state, but the thyroid gland is involuted and easy for the surgeon to deal with. The operative and immediate post-operative course in this group of patients so prepared is smoother and freer of complications than anything I have ever seen before. Following such operations it has been possible to omit both drugs the day of operation, and thus far in a series of 139 cases, we have seen only two persistences and no recurrences of thyrotoxicosis.

I am convinced by what we have observed in the short time since the anti-thyroid drugs were introduced, that they have materially improved the preparation for operation and consequently the risk of operation. One cannot say yet what effect the use of them will have on recurrences or relapses in the years to come.

Let us now observe how the results of prolonged treatment with an anti-thyroid drug alone compare with those of surgery at its best, and in the optimally prepared patient. Although antithyroid drugs have been in use for only three years, there is already a relatively huge literature on them. This was well digested and summarized up to December 1945 in an excellent review by Riker and Wescoe.¹⁰ They give 105 references. In the *Journal of the American Medical Association* for February 9, 1946, there are reports of two surveys of the toxic effects of thiouracil, and an editorial. F. D. Moore¹¹ compiled data from 11 clinics on 1091 patients treated with thiouracil. W. D. Van Winkle, Jr., et al.¹² obtained information by questionnaire from 328 investigators on 5745 cases. More recently still, R. H. Williams¹³ has reported very fully on his own large series of 247 treated cases, and Williams, et al.¹⁴ have reported their toxic reactions.

This material permits it to be said categorically that thiouracil, if given long enough and in sufficient dosage, will produce a remission in any patient with Graves' disease, and that such a remission will continue as long as the drug is continued uninterruptedly. But the pay-off on all this is to be found in the toxic reactions, the recurrences after cessation of treatment, and the cases of aggravation of the ophthalmopathy. The last mentioned seem to be very rare and probably can be dismissed. Certainly they are on the low side of those encountered after thyroidectomy.

On the matter of toxic reactions we find from the papers mentioned above that fatalities attributable to drug are not over 0.5 per cent, agranulocytoses not over 2.5 per cent, and total toxic reactions not over 14.5 per cent. The toxic reactions other than agranulocytosis include leukopenia, drug fever, skin eruptions, lymphadenopathy, salivary adenopathies, and others. Some of them are distressing, but none alarming.

In our own clinic we have used the drug almost exclusively as a preparation for thyroidectomy, and have no experience on toxic side-effects when the drug is used over a long period as treatment per se.

In the matter of recurrence of thyrotoxicosis or relapse, Williams found in 100 cases treated with thiouracil for many months, that 49 stayed well

without treatment after discontinuation during periods of observation from 3 to 21 months. Fifty-one patients had relapses within 0.5 to 5 months, and in 66 per cent of these the relapse occurred within one month. Riker and Wescoe have this to say: "In the more than 1000 cases already reported, approximately 10 per cent continued satisfactorily after the drug was withdrawn. It is noteworthy that in one series of 48 patients in which a thyroid remission was induced by thiouracil therapy for six months or longer, the therapeutic effects continued in 77 per cent of the cases when the drug was withdrawn. There seems to be a relationship between the duration of therapy and the tendency to maintain a thyroid remission after therapy is discontinued. Astwood has advised at least six months of treatment." They further point out that it is important "that all patients who relapse can be retreated successfully with the drug." However, in this connection it should be pointed out that toxic reactions, as in the case of sulfa drugs, probably are more frequent in reëxhibitions of antithyroid drugs than in the original course, and one would not dare reëxhibit the drug in cases in which there had been any idiosyncratic toxic reaction with the first course, or reaction which involved the hematopoietic system.

What then can one say of the relative merits of surgery and of treatment with antithyroid drugs? Nothing with complete finality, of course, but we can weigh the pros and cons in each case. Astwood¹⁵ has pointed out that mortality due to drug is no higher than that due to surgery at its best. In Moore's compilation, deaths due to drug amounted to 0.5 per cent of total treated cases. The operative mortality in skilled hands these days is in about the same neighborhood.

In favor of treatment by drug alone it might be said, therefore, that there is no greater risk, and the ordeal of a surgical operation (or operations) and the cost of hospitalization is avoided. The danger of death from operation, however, does not extend usually over more than 24 hours, whereas the danger of agranulocytosis due to drug, with possible death therefrom, continues as long as the drug is exhibited, perhaps for many months. From the point of view of psychic trauma, not only to the patient but to the doctor, these time relations weigh heavily in favor of an operative program. The long continued close observation of patients on drug therapy alone also imposes a heavy burden on patient and doctor, which is much greater than in surgical treated cases. Persistences and remissions following surgery, moreover, amount to not more than 5 per cent or less. Evidently they are much higher so far in the cases in which drug therapy alone is used.

In comparing surgical with drug therapy, one also must take into account the number of permanent tetanies and vocal cord palseys that follow operation, and any lasting or late deleterious effects of the drug. With regard to the latter it may be said that, except when agranulocytosis is fatal, all toxic drug effects clear up promptly when the drug is omitted. But hypersensitivity to a drug may persist, and there is some experimental evidence to suggest that antithyroid drugs may predispose to later carcinogenesis.

The incidence of tetanies and vocal cord paralyses, transient or permanent, in the hands of expert thyroid surgeons should not be much over 1 per cent each.

The production of myxedema by either method need not concern us. That due to drug clears up when the drug is stopped; that due to surgery can easily be controlled by thyroid. Better a post-operative myxedema than a post-operative persistent or recurrent thyrotoxicosis.

How one will add up these and other pros and cons, will be determined largely by the personal equation. At the moment and until there is more abundant late result data, I feel justified myself in still preferring the operative program to that of prolonged drug therapy. But I fully expect that drugs with less and less toxic effect will be developed, and that one day I might easily prefer drug treatment to operation.

In contrast to that on antithyroid drugs, the literature on the therapeutic use of radioactive iodine is as yet very scanty. The first publication on its use as a tracer in the study of thyroid physiology and as a possible therapeutic agent, that I can find, is that of Hertz, Roberts and Evans ¹⁶ in 1938.

The idea back of treatment of thyrotoxicosis by means of radio-iodine was, of course, that inasmuch as the thyroid gland collects iodine specifically, the giving of radioactive iodine would implant radiation directly within the cells which it was desired to irradiate, and that such treatment, therefore, might be more effective and less injurious to neighboring tissues than roentgen-rays administered from without.

Hertz and Roberts ¹⁷ presented in May 1942, a preliminary report on 10 cases of Graves' disease treated by radioactive iodine, and at the same meeting (American Society for Clinical Investigation) Hamilton and Laurence ¹⁸ reported on three. Hertz and Roberts ¹⁹ have just reported again on their series, which now numbers 29 cases. With doses of radio-iodine varying from 3 to 21 millicuries and followed by courses of ordinary iodine, they claim that 20 of the 29 patients were apparently well three years after treatment.

After Dr. Hertz joined the Navy in 1943, Drs. E. M. Chapman and R. D. Evans ²⁰ studied and treated another series of cases using heavier dosage of radio-iodine, namely, from 15 to 79 millicuries, and no other therapy. Of 22 patients so treated, 20 appear well at the end of two years. The remaining two are improved but still have elevated metabolic rates. In two cases of the last mentioned series, biopsies performed after irradiation showed extensive fibrosis of the thyroid with small scattered islands of hyperplasia of thyroid parenchyma.

What then shall one say of this mode of treatment? Certainly it is an effective way of causing a remission (perhaps permanent) in the thyrotoxicosis of Graves' disease. That much can be stated definitely. Whether it is equal to, or better than, surgical ablation of the thyroid or treatment with antithyroid drugs cannot be said at the present time. The number of cases treated is as yet small, and none has gone over five years. It can be said

that to date there has been no mortality and as yet no evidence of toxic or untoward side-effects except occasional transient roentgen sickness in some of those patients receiving the heavier dosage.

The possibility of late carcinogenic action must not be lost sight of, and it should also be borne in mind that the radioactive iodine not held by the thyroid is excreted in the urine. In the process of excreting the radioactive element, the kidney may be subjected to a considerable amount of radiation which could conceivably damage it. The only evidence we have as yet on renal damage is in the case of one woman with a preceding low grade chronic pyelonephritis which became exacerbated transiently following the exhibition of radio-iodine.

As between programs of equal therapeutic merit, the choice should go to the one which costs the patient the least time, money and annoyance. It is quite possible that from these angles the choice will go to radio-iodine, but the question of relative therapeutic merit, as indicated before, cannot yet be determined.

Yet another non-surgical method of treating Graves' disease, but one which cannot be appraised at all because of paucity of data, is irradiation by roentgen-ray of the pituitary. There is literature on this method going back at least as far as the paper by Borak in 1935.²¹ Until the brief report of W. O. and P. K. Thompson²² in 1944, however, the experience has been largely in the use of the method to treat the ophthalmopathy rather than the thyrotoxicosis, and for that purpose the results have not been impressive. In seven of the 38 cases of the Thompsons, the metabolism dropped permanently to within normal limits. In 16 a temporary reduction in metabolism of from 15 to 52 points was observed. In 15 there was no change.

The rationale of the treatment, of course, is that subduing the pituitary in its thyrotropic activity may attack the disease at a more fundamental level than that of the thyroid.

It is conceivable that irradiation of the pituitary might directly affect the ophthalmopathy in a way treatment aimed at the thyroid would not. But my guess is that roentgen-ray treatment of the pituitary for either the thyrotoxicosis or the ophthalmopathy of Graves' disease will not survive in competition with other methods now available. There is always the danger that one may destroy some other function of the pituitary than the thyrotropic, which one is aiming at. I wrote Dr. E. Perry McCullagh²³ and asked whether any patients he had treated for exophthalmos by irradiation of the pituitary had shown subsequent evidence of hypopituitarism. He replied that in one such case definite anterior lobe hypofunction did develop.

CONCLUSIONS

1. The so-called antithyroid drugs when used in combination with iodine, in the preparation of patients with Graves' disease for thyroidectomy, pro-

vide a more complete preparation than has ever been available before.

2. As between treatment of Graves' disease by thyroidectomy after preparation with an antithyroid drug in combination with iodine, and treatment by prolonged use of an antithyroid drug alone, the author believes that the scales still tip in favor of surgery.

3. Treatment with radioactive iodine is *an* effective way of producing a remission in the thyrotoxicosis of Graves' disease, but any final evaluation of how it compares with other modes of treatment must await observation of more cases and over a longer period of time, particularly with respect to late untoward side-effects, malignancy, renal damage, or others.

BIBLIOGRAPHY

1. KOCHER, T.: Ueber Jodbasedow, Arch. f. klin. Chir., 1910, xcii, 1166.
2. PLUMMER, H. S.: Results of administering iodine in patients having exophthalmic goiter, Jr. Am. Med. Assoc., 1923, lxxx, 1955.
3. MEANS, J. H.: Hyperophthalmopathic Graves' disease, Ann. Int. Med., 1945, xxiii, 779.
4. MEANS, J. H.: How we have treated Graves' disease during a quarter century, Virginia Med. Monthly, 1942, lxix, 535.
5. MEANS, J. H., and AUB, J. C.: The basal metabolism in exophthalmic goiter, Arch. Int. Med., 1919, xxiv, 645.
6. MEANS, J. H., and HOLMES, G. W.: Further observations on the roentgen-ray treatment of toxic goiter, Arch. Int. Med., 1923, xxxi, 303.
7. MOORE, F. D., SWEENEY, D. N., COPE, O., RAWSON, R. W., and MEANS, J. H.: The use of thiouracil in the preparation of patients with hyperthyroidism for thyroidectomy, Ann. Surg., 1944, cxx, 152.
8. LAHEY, F. H., BARTELS, E. C., WARREN, S., and MEISSNER, W. A.: Thiouracil—its use in the preoperative treatment of severe hyperthyroidism, Surg., Gynec. and Obst., 1945, lxxxj, 425.
9. RAWSON, R. W., MOORE, F. D., PEACOCK, W., MEANS, J. H., COPE, O., and RIDDELL, C. B.: Effect of iodine on the thyroid gland in Graves' disease when given in conjunction with thiouracil—a two-action theory of iodine, Jr. Clin. Invest., 1945, xxiv, 869.
10. RIKER, W. F., and WESCOE, W. C.: The pharmacology and therapeutic application of anti-thyroid compounds, Am. Jr. Med. Sci., 1945, ccx, 665.
11. MOORE, F. D.: Toxic manifestations of thiouracil therapy—a coöperative study, Jr. Am. Med. Assoc., 1946, cxxx, 315.
12. VAN WINKLE, W., JR., HARDY, S. M., HAZEL, G. R., HINES, D. C., NEWCOMER, H. S., SHARP, E. A., and SISK, W. N.: The clinical toxicity of thiouracil. A survey of 5745 cases, Jr. Am. Med. Assoc., 1946, cxxx, 343.
13. WILLIAMS, R. H.: Thiouracil treatment of thyrotoxicosis. I. Results of prolonged treatment, Jr. Clin. Endocrinol., 1946, vi, 1.
14. WILLIAMS, R. H., CLUTE, H. M., ANGLE, T., and KENNEY, F. R.: Thiouracil treatment of thyrotoxicosis. II. Toxic reactions, Jr. Clin. Endocrinol., 1946, vi, 23.
15. ASTWOOD, E. B.: Personal Communication, 1944.
16. HERTZ, S., ROBERTS, A., and EVANS, R. D.: Radio-active iodine as an indicator in the study of thyroid physiology, Proc. Soc. Exper. Biol. and Med., 1938, xxviii, 510-513.
17. HERTZ, S., and ROBERTS, A.: Application of radio-active iodine in therapy of Graves' disease, Jr. Clin. Invest., 1942, xxi, 624.
18. HAMILTON, J. G., and LAURENCE, J. H.: Recent clinical developments in the therapeutic application of radio-phosphorus and radio-iodine, Jr. Clin. Invest., 1942, xxi, 624.

19. HERTZ, S., and ROBERTS, A.: The use of radio-active iodine therapy in hyperthyroidism, Jr. Am. Med. Assoc., 1946, cxxxi, 81.
20. CHAPMAN, E. M., and EVANS, R. D.: The treatment of hyperthyroidism with radio-active iodine, Jr. Am. Med. Assoc., 1946, cxxxi, 86.
21. BORAK, J.: Die Behandlung von Hyperthyreosen durch Röntgenbestrahlung der Hypophyse, Strahlentherapie, 1935, liii, 73-89.
22. THOMPSON, W. O., and (by invitation) THOMPSON, P. K.: Treatment of toxic goiter by irradiation of the pituitary, Jr. Clin. Invest., 1944, xxiii, 951.
23. McCULLAGH, E. P.: Personal communication, 1946.

PENICILLIN THERAPY ALONE IN NEUROSYPHILIS: AN ANALYSIS OF CLINICAL RESULTS *

By GEORGE D. GAMMON, M.D., F.A.C.P., and JOHN H. STOKES, M.D.,
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M.D., NORMAN R. INGRAHAM, JR., M.D., PAUL GYORGY,
M.D., ELIZABETH ROSE, M.D., JOHN W. LENTZ, M.D.,
and with the assistance of ABRAHAM ORNSTEEN,
M.D., F.A.C.P., and DONALD SCOTT, M.D.,
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WHEN we began the treatment of neurosyphilis with penicillin in November 1943, we determined to use penicillin alone without fever or arsenic or any other therapy which could influence the course of the disease. This seemed the obvious way to find out what the drug could accomplish, and we have followed this plan with a few exceptions which are noted. In substituting a new régime for the older routines of arsenicals and fever, we felt an urgent obligation to keep a close check on clinical effects as well as the results of blood and spinal fluid reactions. Furthermore, by carefully observing those manifestations of the disease which may be checked or reversed, we hoped to assess more rapidly the results of the new treatment. For these reasons, in this report we consider the effect of penicillin on the symptoms and signs and course of the disease in patients, all of whom were followed for over three months to two years (to November 15, 1945). The diagnostic categories and period of follow-up are listed in table 1.

All patients in the study were examined routinely, originally at one month, later two and, finally, at three month intervals. Although this follow-up program was not always realized, it came close to achievement, since 97 per cent of the cases were followed successfully. A complete neurologic examination was made at each visit, and symptoms were listed on a case card to insure uniformity of information.

As a method of evaluating results of treatment, patients were graded as to abnormality on a 1-4 basis. Following administration of penicillin, the case was graded for change of physical and mental status or lack thereof.

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From the Institute for the Study of Venereal Disease, University of Pennsylvania and United States Public Health Service coöperating, and the Department of Neurology and the Penicillin-Syphilis Panel of the University Hospital. The Institute, the Departments of Neurology, Ophthalmology, Dermatology and Syphilology, and Pediatrics, and the Division of Venereal Disease Control, Philadelphia City Department of Public Health, and the Philadelphia General, Pennsylvania, and Children's Hospitals are represented in the authorship.

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Improvement was expressed in grades 1-4 or "normal," showing the degree, if any, to which the course of the disease had been changed by treatment in the intervals between examinations. The gradation of "worse," 1-4 likewise, was employed, and "unchanged" described an unaltered mental and physical status following treatment. An evaluation of the case as a whole was made on the changes in individual symptoms and signs. For the purpose of reporting the result, grades of improvement were combined into classes "moderate" or "marked" improvement. The same type of grading was used for cases which became worse.

In addition to a full clinical examination, certain special tests were utilized in some cases: tests of visual fields and acuity, electrocardiograms, electroencephalograms, records of speech and of handwriting. Blood and spinal fluid were tested by a battery of technics. The methods employed in the use of penicillin in neurosyphilis by the Penicillin in Syphilis Group of

TABLE I
Follow-Up, Months

Cases	24 to 18	18 to 12	12 to 6	6 to 4
Total 161	33	34	57	37
Paresis 19	5	3	7	4
Tabo-paresis 28	6	2	11	9
Juvenile Paresis 10	1	2	3	4
Tabes 54	8	17	19	10
Meningo-Vascular 31	9	8	9	5
Asymptomatic 19	4	2	8	5

the University of Pennsylvania have been in part outlined in a previous paper,¹ and only essential additional items are here included.

Dosage and Administration of Penicillin. Sodium penicillin in aqueous solution was given intramuscularly every four hours at the beginning of the study. Later, the drug was administered routinely every three hours for a period of eight days until dosage totalled 1.2 to 2.4 million Oxford units. Since May 1945, a new system of dosage, in which the unit is 4.8 million units, has been employed. This is given in three ways: as a single course within eight days; as a single course within 16 days; and as two courses of 2.4 million units each within eight days, the courses being administered seven months apart. In addition to this standard therapy program, there were exceptional instances in which a higher dosage of over 4.8 million units was employed. A few received three courses.

Results. In all the types of neurosyphilis treated with penicillin, the outstanding therapeutic response was a gain in weight which continued for

several months following treatment. This increase amounted to from three to 50 pounds, the majority of patients gaining 15 to 20 pounds, apparently owing to a better appetite and added ingestion of food. A sense of well-being usually accompanied this gain. It is almost as though check was given the infection to which Moxon referred in his aphorism, "Syphilis is a fever diluted by time."

PARESIS AND TABO-PARESIS

In order to compare our results with those of others, it is necessary to emphasize the fact that we were dealing with patients who could be cared for in a general hospital without locked wards. Our cases could be classed in three categories: (1) those with early and mild symptoms of mental derangement who could still do unskilled work; (2) cases with mild residual symptoms in spite of extensive treatment, including fever; (3) cases with severe

TABLE II
Paresis and Tabo-Paresis

Result	Overall Effect				Mental State			
	Par.	Tabo-Par.	Total	%	Par.	Tabo-Par.	Total	%
Improved	14	21	35	74	14	20	34	72
Markedly	6	11	17	36	6	13	19	38
Moderately	8	10	18	38	8	7	15	32
Unchanged	2	5	7	15	2	6	8	18
Worse	2	0	2	4	2	0	2	4
Death	1	2	3	6	1	2	3	6
TOTAL	19	28	47		19	28	47	

paretic-mental breaks of short duration. Thus, of 47 paretics and tabo-paretics, 38 per cent had symptoms for one year or less, and 57 per cent for two years or less. Twenty-six were unable to work because of mental symptoms. Eight had had fever therapy, all except two, two years or more before penicillin treatment.

Considering the results as a whole, table 2 indicates that approximately three-fourths of the cases improved and in 38 per cent this improvement was marked. Fifteen per cent were unchanged, 4 per cent became worse, and 6 per cent died, a total of 25 per cent unimproved. Fever was given shortly after the penicillin treatment to two of the three who died, without influencing the course of the disease.

Mental symptoms improved in 72 per cent of the cases, but 18 per cent were unchanged and 4 per cent became worse; 28 per cent therefore were

unimproved mentally, three of whom were institutionalized. Of the 26 unable to work because of mental changes rather than because of locomotor causes, 17 were able to return to work after treatment.

The most arresting result was observed in the paretics with severe mental break of short duration. The first change, often beginning toward the end of treatment, consisted of an improvement in coördination and tremors. This progress was demonstrated by better speech and handwriting and later by gait. Decrease in tremor occurred in all cases and in about three-fourths tremor disappeared completely. Toward the end of treatment or shortly

TABLE III

Paresis and Tabo-Paresis Cases Unable to Work Because of Mental Changes

Able to go back to work.....	17
Unable to work before or after.....	6
Died.....	3
TOTAL.....	26

afterward, mental improvement began and continued thereafter for some months. The confusion and disorientation commenced to clear, memory improved, delusions began to yield, and hallucinations to disappear. Within three to four weeks after treatment, these gains were obvious to all. The appetite improved and weight was added. These phases of progress continued for the next three to six months after a single course of treatment.

In the cases with less severe mental changes, less obvious and slower results were noted. In the first year following treatment, the patients gained more insight, became calmer, and the ability to hold a job returned.

Date

3/16/44

Penicillin 3/23/44

2nd exam 15 apr

3/30/44

Helen L. Marioni

4/1/44

Helen L. Marioni

4/4/44

Helen L. Marioni

4/12/44

Helen L. Marioni

5/13/44

Helen L. Marioni

FIG. 1. Signatures of a tabo-paretic treated with penicillin.

Reflex activity showed much less alteration. In five cases the increased tendon reflexes became somewhat less active and in two instances a positive Babinski sign disappeared. But in 34 cases, hyperactivity of tendon jerks continued. Pupillary abnormalities were unaffected.

In 19 patients there were electroencephalographic changes. In some the abnormality consisted of slow waves of 2 to 3 per second. In others an activity of 5 to 7 per second was of particular interest, for during or following treatment this 5 to 7 per second activity tended to speed up toward the normal alpha pattern of 9 to 11 per second. Of the 19 cases cited, 16 were reëxamined and 12 showed improvement following therapy. The evidence furnished by this objective test clearly indicates that an alteration of cortical activity may be observed following penicillin therapy. A more detailed report with Dr. Donald Scott is being made elsewhere.

Taking these results as a whole, in this type of neurosyphilis there is clear-cut evidence that penicillin has an active therapeutic effect.

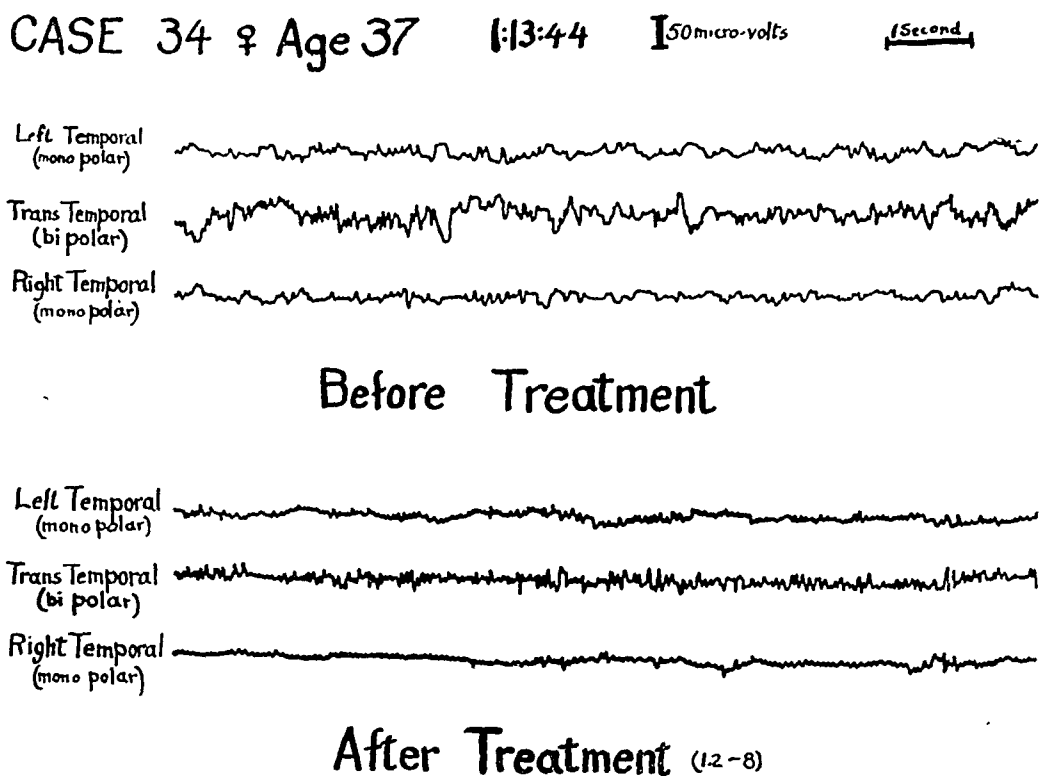


FIG. 2. Electroencephalogram of paresis. Decrease in slow-wave activity after treatment with penicillin.

JUVENILE PARESIS AND TABO-PARESIS

There were 10 cases in this category, and the results of penicillin administration, as of other therapeutic measures used heretofore, were less satisfactory than in acquired paresis and tabo-paresis.

The overall evaluation in five juvenile paretics and tabo-paretics remained unchanged under penicillin therapy; one patient became worse. In this patient, who was observed carefully over a long period of time with frequent psychological tests and under instruction in the Psychology Department of the University, there was slow deterioration which was not arrested by fever therapy employed after penicillin proved inadequate (table 4).

Four of these juvenile cases improved moderately in their general condition and mental status. Station and gait in the congenital syphilitic patients were unaffected by penicillin therapy except in one instance, and tremors were unaltered. Speech was moderately improved in one instance and deteriorated in another. The drug had no effect upon sensory abnormalities or the condition of the pupils. A definitive evaluation of treatment in this type of patient, particularly in comparison with other methods, cannot be made at this time, but the results do not suggest that penicillin has solved this most difficult problem of neurosyphilis.

TABLE IV
Juvenile Paresis and Tabo-Paresis

	Overall Effect	Mental State
Improved		
Moderately	4	4
Markedly	0	0
Unchanged	5	4
Worse	1	2
Death	0	0
TOTAL	10	10

TABES

In the complex symptomatology of tabes, there can be seen a mixture of mechanisms representing both destruction and stimulation. Pain is the result of stimulation and should respond promptly to any effectual therapy which stops the stimulation. Ataxia, incontinence, impotence and reflex loss are the evidence of destructive processes which advance slowly. On these latter symptoms, effectual therapy can become apparent only if it checks the progress, and this requires a time-scale of years.

We chose for study, therefore, chiefly tabetics with typical tabetic lightning pain, and despite the obvious difficulties in an analysis of this subjective symptom, we believe that our observations are, in the main, authentic. Patients were questioned in detail on the duration, character, location, severity and frequency of pains before treatment. Following penicillin administration, each was given a mimeographed sheet on which he kept a pain

calendar with details of location and severity and medication required for relief. Most of the patients conscientiously kept the data, and from the charts and the frequent interviews, we assembled the data on which we base these statements.

The survey showed that (table 5) in the 55 tabetic and tabo-paretic patients, there were 40 who had lightning pains before treatment. There was some degree of improvement in 82 per cent following penicillin therapy regardless of the number of courses administered. In 15 per cent pain disappeared completely, and in approximately one-third of the cases the improvement was marked, while in another one-third it was of moderate degree. The pains were unchanged in 12 per cent and became worse in 17 per cent of patients. Of 15 patients in whom no pain had been present, four developed pain during or after administration of penicillin, a Herxheimer-like reaction which sometimes was seen in the use of penicillin. Ten patients

TABLE V
Tabes and Tabo-Paresis with Pain

Pain Before Treatment	Pain After Treatment						
	Improvement				No Improvement		
	None	Marked	Moderate	Total	Unchanged	Worse	Total
Moderate 24	6	4	9	19	3	2	5
Severe 16	0	9	5	14	2	0	2
TOTAL 40	6	13	14	33	5	2	7
Per cent	15	32.5	35	82	12.5	5	17.5
No Pain 15					11	4	
TOTAL 55							

had recurrence of pain following temporary relief from the first course of treatment. These were retreated on the basis of pain. Four of these had two or more relapses. The duration of pain did not appear to influence its response. There was no significant difference in the results of treatment in cases in which the tabetic pain had been present more than or less than five years.

In view of the occasional Herxheimer exaggeration of pain and of the more frequent relief of pain, it appears to us that penicillin is acting on the process responsible for the pain. The effects are greater than might be expected as a result of spontaneous remission, and on the whole compare well with results of other forms of therapy.

In three cases with gastric crises, definite improvement was noted in two and slight improvement in another. These cases required large amounts

of penicillin and were retreated if the pain recurred. One man received intraspinal therapy. It is much too early to know if these effects will prove permanent. Brief abstracts of these cases follow:

One patient (CM) suffered so severely from pain that he developed suicidal tendencies. However, immediately after the first treatment with penicillin, the gastric pain subsided. There remained only a mild prickling pain in the epigastrium occurring at approximately three day intervals and lasting for about 25 minutes. On two occasions this was associated with nausea. Codeine controlled this type of pain whereas the earlier pain had responded to morphine only. This patient is greatly improved.

In a second case (CT) prior to therapy the pain had recurred every three weeks. Following total dosage of 10 million units, 340,000 units of which were given intrathecally, the intervals between the crises became longer, and although there is some question of psychic overlay in this patient, he insists he is improved by treatment and appears to be improved.

TABLE VI
Gastric Crises in Tabes; End Result

Case	Yrs.	Pain	Vomit	Length	Frequency	Dose	Follow-up (Mo.)
CMA	3	Severe; slight	Severe; none	2-3 days 2 hours	Weekly; 6 mo.	10	15
EB	$\frac{3}{4}$	Mild; none	Mild; none	1-2 wks. none	Monthly; none	13.6	12
CT	3	Severe; less	Severe; less	3 weeks 1 week	3 weeks 6 weeks	10	10

The first line describes conditions before treatment; the second line after treatment.

In case 3 (EB) there had been a great deal of treatment, including Swift-Ellis and fever therapy, prior to penicillin administration. These proved ineffectual. Six months after the initial administration of 1.2 million units of penicillin, the attacks of vomiting, which had previously occurred every two or three weeks, ceased. However, after 13.6 million units of penicillin, the daily nausea persisted in this patient although her general condition improved.

In the remaining symptoms of tabes, no very striking changes were noted, and when the patients claimed some improvement, it was usually of a nature and degree which was more obvious to them than to the examiner. Ataxic gait is an illustration; in only two cases could definite improvement be seen although 12 more claimed they walked better. Seven patients considered themselves worse.

Impotence, partial or complete, was present in 19 and six of this number claimed some improvement in function. No deterioration of normal function occurred. Urinary incontinence, partial or complete, was present in 13,

five of whom thought they had better control after treatment. In 33 without previous evidence of bladder difficulty, five developed some disability following therapy, and in four of these this was clear evidence of an unfavorable course of the disease.

Pupillary abnormalities were unaffected and absent reflexes were unchanged. No patient lost reflexes or developed pupillary changes while under observation.

In some cases a complex mixture of improvement and progression could be seen. In the cases in which pain improved, ataxic gait became worse in six, improved in three, and remained unchanged in one. One patient improved in sexual ability but became worse in gait, bladder and mental functions. In four cases, improvement occurred in gait, bladder and potency, but lightning pains, absent before treatment, developed. These mixed responses increase the difficulty in assessing the value of therapy and emphasize

TABLE VII
Tabes Dorsalis

Symptoms and Signs	Abnormal before Treatment			Normal before Treatment	
	Better	Same	Worse	Worse	Same
Ataxia 33	18	12	4	3	21
Impotence 19	6	13	None	None	35
Urinary Incontinence 18	5	8	0	5	28
Pupils Abnormal	None	All	None	None	All
Reflexes	None	All	None	None	All

the view expressed above that a long period of observation is necessary. Apart from the effect on pain, then, in tabes very little improvement has been seen. One has the impression that these cases lack the elasticity of response seen in early paretic cases.

SPINAL SYPHILIS

This type of syphilis, which is sometimes combined with tabes, is the result of vascular disease of the cord at one or more levels. Fluctuation in signs may be abrupt and there is a special hazard of transverse myelitis if treatment is too enthusiastic. Fortunately, some cases declare themselves beforehand by girdle pains on the trunk, sensory impairment to the level of the pain, and positive Babinski signs in the lower extremities; with this may go the absent reflexes and posterior column signs of tabes. One patient of this kind (DB) developed a transverse myelitis in the first 36 hours of treatment, became weak in the legs, but in the end improved until he was better off

than before. Another case went steadily downward despite treatment. Low initial dosage of penicillin should be given to these cases.

MENINGO-VASCULAR SYPHILIS

The yardstick for therapy in this group is the spinal fluid and blood response. Clinical evaluation rests on whether the disease gradually progresses. Of the 31 cases, three died, one in the Hospital and another at home unobserved. A third was killed in an accident. One case originally diagnosed meningo-vascular became frankly paretic. Three other cases may have had a progression of the disease, but the diagnosis was based on findings which are not conclusive. In one patient (WL) pupil reactions were less prompt; in another (DB) loss of deep pain in the Achilles tendon de-

TABLE VIII
Spinal Fluid under Penicillin
(Results in Per cent)

Type		Grades 3, 4 N and NN	Normal NN	Worse
Paresis	16	62	31	4
Tabo-Paresis	37	58	39	
Meningo-Vascular	33	73	45	
Tabes	51	86	57	
Congenital	16	81	63	
Asymptomatic	30	70	60	

Grades 3 and 4 mean improvement in three or four of the following components of the spinal fluid: cells, protein, Kolmer test or colloidal mastic.

NN (near normal) signifies spinal fluid with cell count 5-10, protein 20-40, negative Kolmer test, and colloidal mastic 1111000000.

veloped in the 18 months of observation; in a third (AH) vibratory sensation became slightly impaired. In four cases, then, the disease obviously became worse.

Little comment is required concerning recovery from strokes affecting various parts of the brain. In eight cases the recovery differed in no way from the behavior of nonsyphilitic cases. Headaches were greatly reduced following penicillin therapy.

Convulsions. Seizures occurred in two meningo-vascular cases, five paretics, four tabo-paretics, one tabetic, and two congenital paretics, a total of 14 cases. Two of these patients had partial continual epilepsy which was undoubtedly the result of cerebral hemorrhage, for hemiplegic signs developed as well as homonymous field cuts and sensory loss, and the spinal fluid became xanthochromic. In one of these, the signs developed in the first 24 hours of treatment, in the other just before treatment. The latter

was treated with penicillin alone, and the twitching slowly subsided in 36 hours, probably without relation to this therapy. Anticonvulsants have been necessary to control both of these cases, and in the whole group there is only one case which has not required anticonvulsant medication. Penicillin therefore will not prevent these seizures.

Asymptomatic Cases. In the period of observation, one patient of the 21 developed pupillary abnormalities. The others remained without signs or complaint.

DOSAGE

Recent studies on the composition of penicillin have divided it into several fractions called G, F, K and X. Of these, K is less effective in syphilis than the other fractions. Throughout the period covered by this investigation, the relative percentage of these fractions has changed, but in unknown

TABLE IX

Effect of Dosage (Million Units) on Overall Evaluation in Paresis and Tabo-Paresis

		1.2	2.4	4.8	2.4+2.4	1.2+2.4 or 2.4+1.2	Multiple High
Improved	35	3	7	8	3	5	9
Total Unimproved	12	1	5	1	2	1	2
Unchanged	7	1	1	1	2	—	2
Worse	2*	—	2	—	—	—	—
Died	3	—	2	—	—	1	—

* One case 3.0.

Multiple high includes doses above 4.8 and up to 10 million. (Some cases given 3 courses of treatment.)

amounts. Today's penicillin has more K and is therefore less effectual in syphilis than the 1943 vintage. Relapse rates in early syphilis reflect this.

This fact, unfortunately, vitiates any analysis of dosage effects. Furthermore, no valid data on dosage can be obtained until we have an unvarying compound. Fortunately, as the study progressed we gave larger doses, partly because we had more drug available, and this may have offset the declining antisyphilitic properties.

Neither the spinal fluid findings nor our data on clinical results in paresis and tabo-paresis showed any significant difference between the single course of 1.2, 2.4 or 4.8 million, nor between any of these and multiple courses, nor between low (to 4.8) or higher (above 4.8) dosage.

An analysis of dosage in relation to the effect on tabetic pain reveals only that the patients with most severe pain received the largest amounts of penicillin in repeated courses until some measure of relief was secured. Larger

doses were required here than in other cases, often from 6 up to 12 million units.

Despite current uncertainties, this can be said. If the patient can be kept under close and continuous observation, it is safe to give initial doses of 2.4 or 4.8 million units. If paretics with mental breaks fail to improve in four to six weeks, more penicillin, or fever should be given. In less urgent cases, retreatment should be given in four to seven months if the response has been inadequate. Tabetic pains may require higher doses, up to 12.0 million units and multiple courses.

Decision to retreat was made on the basis of these factors: failure of spinal fluid to become normal; failure of reversible symptoms to respond; relapse in spinal fluid; relapse or progression in symptoms.

Clinical and spinal fluid checks should be made at three month intervals during the first year and six month intervals thereafter.

Neural Herxheimer Reactions. During the first 24 to 36 hours of treatment, some patients showed an exaggeration of neural signs or symptoms. Quite frequently in parietic cases a mild increase in mental abnormalities was seen. Severe and dangerous reactions occurred in six cases. One nearly died in convulsions (CF), one bled into his brain and developed partial continual epilepsy, and two others had milder seizures. One of these (HM) also became confused and agitated and had hallucinations for the first time. All of these four patients, however, ultimately became very much better. Another parietic (SA), however, became maniacal and ultimately died.

Two cases developed transverse myelitis but ultimately recovered and even improved. Reference to one of these cases (DB) has been made above. Increase in tabetic pains occurred in four cases; in one, in each of two courses of treatment (JA).

To offset these reactions we cut the original four to six doses to 6,250 or 12,500 units and since then have had only one reaction which developed during retreatment. If a severe reaction occurs, treatment should be interrupted for one to two days and resumed at low dosage level. Special care is required in spinal syphilis.

From these experiences, it is clear that penicillin can be a dangerous drug and must be used with caution.

Fever, when it occurred, was not over 100° or 101° F. and lasted 12 to 24 hours. It has been too slight to have influenced the disease.

DIFFERENTIAL DIAGNOSIS

As with Medicine, syphilis is the tutor of Neurology. In examining some 300 neurosyphilitics, difficult problems in differential diagnosis inevitably arise. These fall into three classes: (1) the type of neurosyphilis, (2) syphilis combined with other disease, and (3) syphilis versus other disease, including reaction to penicillin. In regard to the first category, one cannot but be impressed with Wilson's dictum that neurosyphilis is pathologically

one and indivisible. The diagnoses herein made are based on the chief clinical features of the case.

In the second category, errors can only be avoided by constantly raising the question: Is any other disease present? Failure to do so led to missing an angle tumor in an old tabetic. The early papilledema was attributed to syphilitic neuritis. A spinal cord tumor was diagnosed in a syphilitic from the clue of yellow spinal fluid. This had been observed repeatedly over several years without comment. Especially difficult is the differentiation of non-syphilitic psychoses in syphilitic patients, particularly an evaluation of the nature of arteriosclerotic brain disease in a syphilitic.

In the third category are a group of cases without syphilis which show positive spinal fluid reactions. The blood reactions are negative and the patient has never had antisyphilitic treatment. We have seen this in the presence of a spinal cord tumor in three cases. In all of these spinal fluid protein was high. We have also encountered it in other diseases of the nervous system including acute multiple sclerosis. In one case of this kind, spinal fluid tests gave a biologically false-positive reaction. In another case with hemiplegia, the reaction cleared up at the end of treatment. The nature of these reactions is not clear but the important point is that they occur in nonsyphilitic patients. Further study of these will be made.

SPINAL FLUID AND BLOOD

The observations on spinal fluid and blood in this material, and a few additional cases, have been analyzed in a recent paper by John H. Stokes, et al., and only the salient points will be noted here.

Successive evaluations in May and October, 1944, and November, 1945, have shown that an increasing number of fluids became normal:

	Grade of improvement	
	3 and 4	Normal NN
May, '44	56	2.6
October, '44	33	26.0
November, '45	18	62.0

A previous analysis in terms of dosage and numbers of courses had demonstrated a trend toward better results with higher doses than lower doses and better results with two courses than one course. In the present material, however, this trend was not apparent. Tables 10 and 11 emphasize the similarity of effect of one course and of doses below and above 4.8 million units. Further study will be necessary to obtain conclusive evidence on these points. The factors which we know modify the result are the length of follow-up and the type of case, as well as total dosage and the time over which it is given. Our present routine of a standard of 4.8 million units.

described above, may provide adequate evidence when sufficient follow-up time permits analysis.

The results for various types of cases are seen in table 8. Asymptomatic and congenital cases gave the best response and paretics the least response.

The time course of change in the spinal fluid is of interest. Cells and protein dropped quickly and mastic and Kolmer tests followed. The major part of the change occurred in the first four months, but with longer observa-

TABLE X
Spinal Fluid Response in Relation to Dosage and Period of Observation*
A Comparison of Low and High Dosage

Amount of Treatment		<i>Low Dosage</i> 1.2 to Less than 4.8 Million in 1 or 2 Courses; 92 Cases		<i>High Dosage</i> 4.8 to 10 Million and over in 1 to 4 Courses; 83 Cases	
Observation 120-364 Days	Slight Imprvt.	10		7	
	Marked Imprvt.	10	Strikingly improved 35 cases 69 per cent	14	Strikingly improved 37 cases 71 per cent
	NN and Normal	25		23	
	No Change	3		5	
	Worse	3		3	
Observation 365-599 Days	Slight Imprvt.	3		6	
	Marked Imprvt.	4	Strikingly improved 24 cases 84 per cent	6	Strikingly improved 14 cases 67 per cent
	NN and Normal	20		8	
	No Change	2		1	
	Worse	0		0	
Observation 600 Days and Over	Slight Imprvt.	1		1	
	Marked Imprvt.	1	Strikingly improved 10 cases 84 per cent	2	Strikingly improved 9 cases 90 per cent
	NN and Normal	9		7	
	No Change	1		0	
	Worse	0		0	
Remarks		75 per cent strikingly improved		72 per cent strikingly improved	

* This includes all neurosyphilis, a total of 175 cases with abnormal spinal fluids.

TABLE XI

Spinal Fluid Response to Penicillin in Relation to Number of Courses*
By Period of Observation and Irrespective of Dosage

Number of Courses		1—81 Cases		2—75 Cases		3—16 Cases	
Observation 120–364 Days	Slight Imprvt.	7		9		1	
	Marked Imprvt.	13	Striking imprvt. 47 cases 78 per cent	8	Striking imprvt. 22 cases 60 per cent	2	Striking imprvt. 2 cases out of 3
	NN and Normal	34		14		0	
	No Change	2		5		0	
	Worse	5		1		0	
Observation 365–599 Days	Slight Imprvt.	1		6		1	
	Marked Imprvt.	4	Striking imprvt. 14 cases 88 per cent	4	Striking imprvt. 19 cases 70 per cent	2	Striking imprvt. 5 cases out of 6
	NN and Normal	10		15		3	
	No Change	1		2		0	
	Worse	0		0		0	
Observation 600 Days and Over	Slight Imprvt.	0		1		1	
	Marked Imprvt.	0	Striking imprvt. 4 cases 100 per cent	2	Striking imprvt. 9 cases 82 per cent	2	Striking imprvt. 6 cases out of 7
	NN and Normal	4		7		4	
	No Change	0		1		0	
	Worse	0		0		0	
Remarks		80 per cent striking improvement		67 per cent striking improvement		81 per cent striking improvement	

* 3 cases given 4 courses (1 slightly improved, 1 no change, 1 normal), making the case total of 175, were not included, as numerically insignificant.

tion it is apparent that the improvement continued over several months in some cases.

There was less response in blood than in spinal fluid and there was no recognized correlation between them. Only 30 per cent of cases with initially sero-positive bloods improved in those in which the spinal fluids became normal (82) or were markedly improved (115). The proportion of

serologic failure, despite marked spinal fluid improvement, was about 46 per cent. The blood findings had little significance for symptomatic or spinal fluid results.

A comparison of the results of malaria and other forms with penicillin therapy must eventually be made. With only two years of penicillin treatment, it is obvious that no final conclusions can be drawn. The results of the Coöperative Clinical Group were compared with our penicillin results and are taken from the article by Stokes et al. in the *Journal of the American Medical Association*. Results of penicillin on spinal fluid were better than malaria or chemotherapy in asymptomatic neurosyphilis and were of the same order of magnitude in the other types. Clinical results to date do not yet

TABLE XII

Comparison of Reported Coöperative Clinical Group Results with University of Pennsylvania Penicillin Results

Spinal Fluid Reduced to Normal (Results in Percentages)					
	Tabes	Dementia Paralytica with Tabes	Dementia Paralytica	Meningo- Vascular	Asymptomatic
Routine	29	17	11	43	36 (1 yr.)
Swift-Ellis	49	28	18	59	39.2 (1 yr.)
Tryparsamide	40	46*	17	47	15 (1 yr.)
Malaria	22	12	9	0*	1.2 (1 yr.)
Penicillin†					
Normal	33	30	0	30	53
Near Normal	24	15	31	15	7
TOTAL	57	45	31	45	60

* Less than 20 cases.

† Fifty-eight per cent of these cases observed 1 year or less, 29 per cent up to 600 days.

equal those of malaria, but with lengthening experience, it seems probable that penicillin results will approach those of older routines. At the present time we consider it a safe first therapy.

SUMMARY AND CONCLUSIONS

1. One hundred sixty-one cases of neurosyphilis were treated with penicillin alone from November 1943, to July 1945. The results, as measured clinically and by blood and spinal fluid change, showed that penicillin is an active therapeutic agent.

2. The greatest effect on symptoms and signs occurred in the mental breaks, the incoördination, tremors and speech defects of paresis and in the lightning pains of tabes. Fixed pupils, absent reflexes and other signs of destructive lesions did not improve.

3. Spinal fluid abnormalities were particularly responsive to penicillin. The effect on asymptomatic cases was greatest and on paretics least. Blood responses are less than spinal fluid responses.

4. Penicillin is the first choice for the first treatment of neurosyphilis. This statement may be qualified for severe paretics. In these, failure to improve promptly indicates further treatment, either more penicillin or fever. Dose schedules are discussed in the light of the various factors involved including the changing character of penicillin. Adequate clinical and spinal fluid follow-up is essential.

CASE REPORTS

RR, white male, 52 years of age; paresis with marked clinical and serological improvement.

This patient, in 1943, developed attacks of epigastric pain and paresthesias of the ankles. He was unable to work because of progressive forgetfulness and tremors of the hands.

On February 10, 1944, neurological examination showed unequal pupils which reacted sluggishly to light, grossly slurred speech and tremors of the face. Coördination of both upper and lower extremities was greatly impaired, especially on the right side.

On February 24, 1944, treatment with penicillin was begun and a total of 2.4 million units was given within an eight day period, without untoward reaction.

On March 22, 1944, the patient was reëxamined and his mental state proved to be one of mild euphoria, but station and gait appeared to be normal. The Romberg test was negative. There was slightly impaired coördination of both extremities and a tremor of the left upper extremity when the hands were extended. Tendon reflexes were equal and slightly increased. Sensations of touch, pain, position and vibration were normal. There was no change in the pupils. There was tremor of the right side of the face and definite slurring of speech. The patient was not able to work.

Reëxaminations were made at approximately two month intervals throughout 1944 and 1945 and on October 31, 1945 the patient was found to be mentally clear, with a negative Romberg. His coördination and reflexes were normal. He had no epigastric pain and the paresthesia of the ankles had been relieved. There remained a slight tremor of the lips and tongue.

The most recent examination, February 20, 1946, revealed a return to a practically normal physical and mental status except for the inequality of the pupils. However, vision, too, had improved, and the patient had returned to work. The original spinal fluid report showed: Wassermann 4444; protein 75; mastic 4555543110, while the test of October 31, 1945, showed Wassermann 0000; protein 20; no cells; mastic 1111000000.

It need not be emphasized that in this case both the serological and clinical remission was of marked degree.

HM, female, white, married, 47 years of age; taboparesis. Symptoms increased during treatment but ultimately improved.

In February 1944, this patient developed severe mental changes with delusions of paranoid trend. There was disability of gait so marked as to cause falls on several occasions. In one fall the patient broke several ribs. There was dribbling from the bladder.

The past history of the patient is irrelevant except that between the ages of 20 and 29 she had had epileptic seizures with unconsciousness and tongue biting.

Neurological examination showed considerable weakness of the lower extremities with bilateral absence of the patellar and Achilles tendon reflexes. Biceps and triceps reflexes were normal. The fundus of the eye could not be seen owing to opacities in the lens. The right pupil was larger than the left but both pupils reacted sluggishly to light and accommodation. Extraocular movements were normal. There was no facial weakness, but a tremor of the lips was present and the tongue protruded in the midline with marked gross tremors.

On March 23, 1944, the patient was given penicillin therapy, a total of 4 million units. On the ninth day of treatment she developed an attack of unconsciousness lasting for a few minutes. This, apparently, was a Herxheimer reaction to the drug.

At the end of treatment, although still ataxic, the patient was able to get up and walk about. However, during treatment the mental condition deteriorated and she developed auditory delusions with confusion.

Reexaminations were made at intervals in 1944 and 1945 and it was decided to repeat the penicillin dosage. September 17, 1945, 4.8 million units were administered. The improvement in gait and other physical and mental symptoms continued at slightly accelerated pace. On examination August 22, 1945, the gait had become almost normal, the mental and physical status had improved markedly. The reflexes were practically normal. There was almost no slurring of speech with test phrases. Her handwriting had improved markedly. The original spinal fluid showed: Wassermann 4444; protein 47 and a mastic 443221000 while that of April 17, 1945 showed: Wassermann 0112; one cell; protein 20; and mastic 2221100000.

CF, female, white, married, 37 years of age; paresis. Severe convulsions during treatment. Marked improvement later.

In November 1943, the husband noticed personality and behavior changes in this patient who became careless in her dress and of seclusive habit.

A year earlier she had been struck by a trolley and hospitalized for severe contusions and lacerations on the right side of the head in the region of the frontal bones. She was discharged later from the hospital in normal condition. The original diagnosis was multiple cerebral concussions.

After her return home she developed auditory hallucinations and was confused. She was again hospitalized January 7, 1944. She was conscious and cooperative but showed a loss of recent and remote memory and Romberg test was negative. Coordination of the upper and lower extremities was normal except for a minimal tremor of the hands. The tendon reflexes were somewhat diminished, the triceps increased. The patellar and Achilles reflexes were markedly exaggerated. There was no ankle or patellar clonus. Sensation of touch, pain, heat, and temperature was normal.

The pupils were equal and regular and reacted to light and convergence. There was a fine tremor of the upper lip. There was tremor of the tongue and greatly impaired speech.

On January 19, 1944, penicillin was administered, and after receiving 23,000 units, the patient developed a series of right-sided convulsive attacks involving the face, and, at times, the arms and legs. She appeared to be aphasic. There was a bilateral Babinski sign and slight facial weakness.

Penicillin was discontinued and the attacks were controlled with oxygen. The patient appeared to be extremely ill during the following 24 hours. The blood pressure fell to 80 mm. Hg systolic and 40 mm. diastolic, she became cyanotic and there was twitching of the right upper extremity.

Within two days, however, the condition cleared and there was no weakness of upper or lower extremities or face. The Babinski sign had disappeared. Penicillin was administered again and she was given 1.2 million units without further untoward reaction.

The ultimate reaction to the drug was dramatic. Tremors of the extremities diminished, and the hallucinations disappeared. Memory, apparently, was completely restored. The only remaining symptoms were slight tremors of the facial muscles, the tongue and upper extremities.

By October 11, 1944, the patient had gained 27 pounds and was practically in normal mental and physical condition.

Another examination on January 23, 1946, showed continued improvement. The patient was able to hop on either foot; coördination and reflexes were normal. The pupils reacted equally to light and convergence. The only complaint was continued slight tremor of the facial muscles.

JA, white, female, 36 years of age; tabes. Lightning pains brought on by treatment on two occasions.

In October 1943, this patient developed paresthesias of the third and fourth fingers of the right hand. The toes of the left foot became somewhat stiff and numb.

Neurological examination at admission January 1944, showed the pupils were equal and reacted to light and convergence. There was a slightly positive Romberg test. Tests of coördination and strength were normal. There was no definite impairment of sensation, vibration, touch or position. There was generalized hyporeflexia. Biceps reflexes were greatly diminished, the triceps less so. The abdominal reflexes were present. No patellar or Achilles jerks were obtained. There was a negative Babinski response.

This patient received 1,200,000 units of penicillin within eight days. After the fourth injection, hives appeared over all the body. Treatment was suspended temporarily and the hives subsided.

At the end of treatment, shooting pains of tabetic type and short, stinging pains affected the region of the right shoulder, the upper extremities, calf of the leg and anterior surface of the thigh. There was cramping of the tendons of toes, in the left calf and posterior thigh muscles. These pains subsided in approximately three weeks.

The paresthesia of the toes and the headaches disappeared following therapy.

On examination one month later, February 16, 1944, there was no essential change in the patient's symptoms except increased sensation in the toes, and a second course of 2.4 million units of penicillin was administered. Pains recurred during the second course of treatment and there was very slight residual cramping of the fingers.

On October 10, 1945, the patient stated the lightning pains were less severe and less frequent. There was still a slightly positive Romberg and the right fourth finger was still painful. Otherwise, the patient was in excellent condition.

There was no recurrence of the hives or the lightning pains.

DB, white, male, married, 38 years of age; Herxheimer effect; transverse myelitis with recovery.

This patient was in good health until the summer of 1942 when he developed numbness and paresthesia of the medial aspect of the thighs and genitalia. His local physician gave him a course of 58 injections, apparently with little effect. Seven months later deep, sharp pains of the lower extremities appeared, which came on in bouts and lasted two to three hours. More recently there was also diplopia.

Neurological examination revealed an ataxic gait, a positive Romberg, absent knee and ankle jerks and impairment of pain, temperature and vibration sense as far as the iliac crest. There was also ptosis of the left lid, sixth nerve weakness and sluggish pupils. There was tremor of the tongue and the speech was slurred.

The skull plate was negative and the visual fields were normal while the diplopia fields revealed a right rectus palsy. The blood and spinal fluid serologic reactions were positive with a parietic colloidal mastic curve. The electroencephalogram showed no significant abnormalities.

On January 24, 1944, the patient was placed on penicillin, 25,000 units every four hours. On January 27, 1944, the man complained of considerable pain and increased weakness of the legs. Patches of dermatitis appeared on the right lower leg, and macular eczema on the extensor surfaces of the arm and buttocks. There was a positive Babinski response in the lower left extremity when the patient was lying down but not when sitting up.

Although the original neurological findings indicated a diffuse and patchy meningo-vascular syphilis with considerable posterior column involvement and a typical parietic cerebrospinal fluid, the greatly accentuated symptoms following therapy seemed to be the expression of a Herxheimer-like reaction.

Penicillin was discontinued to be resumed February 2, 1944, the 25,000 units being reduced to 12,500 units for two doses after which the 25,000 unit dosage again was administered until 1,200,000 units of the drug had been given without further untoward reaction.

The patient was examined thereafter at frequent intervals and found to be slowly improving clinically and serologically. The tabetic pains still were frequent although less severe in character and another course of 2.4 units of penicillin was given December 11, 1944. There was no Herxheimer effect during retreatment.

The most recent examination, November 14, 1945, showed there was less pain and less weakness in the limbs. There was still a positive Romberg. The mental condition was clear; sensation was normal and there were no tremors.

The spinal fluid findings of February 2, 1946, showed no cells, a negative Wassermann, protein 10 milligrams, and mastic of 1110000000.

HH, male, colored, married, 38 years of age; paresis. Subarachnoid hemorrhage during treatment. Subsequent improvement.

In 1940 this patient went to Pennsylvania Hospital because of convulsions. A diagnosis of paresis was made and the patient given 54 hours of fever therapy. Tryparsamide was also administered.

In 1944 the patient returned to Pennsylvania Hospital because of attacks of vomiting without diarrhea. The serologic reaction was positive at this time. The history showed that in 1943 the patient had developed a shuffling gait, that he stumbled easily and that the convulsive seizures still were present. About April 1944, marked mental changes with hallucinations and delusions developed, and the patient became incontinent. His local physician had him admitted to Philadelphia Psychiatric Hospital where he was given 12 injections of typhoid vaccine. His response was unfavorable and at the request of his physician on June 1, 1944 he was admitted to the Hospital of the University of Pennsylvania where the original neurological examination showed him to be definitely psychotic.

On June 19, 1944, penicillin was started and two days later a generalized convulsion occurred. This heralded a subarachnoid hemorrhage and a left hemiparesis. Therapy was interrupted a few days and then resumed for a total dosage of 2.4 million units.

Neurological examinations at frequent intervals thereafter revealed steady improvement in his physical and mental condition except that occasional convulsions still occurred. On January 15, 1945, 1.2 million units of penicillin were administered.

No convulsive seizure or other type of Herxheimer reaction followed this therapy and all examinations since have showed the patient's steady improvement.

On examination February 6, 1945, the man was greatly improved, although not normal, mentally and physically, and the Romberg sign was negative. He has now returned to work. Residual signs of his disease were slight tremor of the tongue and of the left facial muscles. However, anticonvulsant medication was necessary to control his seizures.

The results which have been presented in this paper must be interpreted in light of the fact that from June, 1943, the date of inception of the study, to the present, commercial penicillin has been a changing mixture of various substances. The content of "impurities" has gradually decreased as potency, in terms of units per mg., has increased. The relative amounts of the several identified penicillin fractions G, F, X, and K have likewise varied from time to time. Those two changes, and perhaps others, suggest that therapeutic efficacy may not have remained constant; and that it may be significantly different today from what it was originally. It is now impossible to assess the extent to which these changes may have affected the results here reported.

BIBLIOGRAPHY

1. STOKES, J. H., STEIGER, H. P., GAMMON, G. D., STEELE, W. H., BEERMAN, H., INGRAHAM, N. R., GYORGY, P., ROSE, E. K., and LENTZ, J. W., with the technical assistance of VERA MAYER STEIN and EMILY STANNARD: Penicillin alone in neurosyphilis, Jr. Am. Med. Assoc., 1946, cxxxi, 1-7.

Previous reports of this work have been made as follows:

- GAMMON, G. D., STOKES, J. H., LENTZ, J. W., STEELE, W. H., ROSE, E. K., SCOTT, J., SCOTT, D. M., JR., and ORNSTEIN, A.: Immediate and early effects of penicillin on syphilis of the central nervous system, Trans. Am. Neurol. Assoc., 1944, 65-69.
- GAMMON, G. D., STOKES, J. H., BEERMAN, H., INGRAHAM, N. R., LENTZ, J. W., MORGAN, H. G., STEELE, W., and ROSE, E. K., with the technical assistance of VERA MAYER: Penicillin in neurosyphilis: effect on blood and spinal fluid, Jr. Am. Med. Assoc., 1945, cxxviii, 653-654.
- STOKES, J. H., GAMMON, G. D., BEERMAN, H., INGRAHAM, N. R., JR., LENTZ, J. W., MORGAN, H., STEELE, W., ROSE, E. K., and GYORGY, P.: Penicillin in late syphilis, Am. Jr. Syph., Gon., and Ven. Dis., 1945, xxix, 313-333.
- STOKES, J. H., STERNBERG, T., SCHWARTZ, W. H., MAHONEY, J. F., MOORE, J. E., and WOOD, W. B., JR.: The action of penicillin in late syphilis, Jr. Am. Med. Assoc., 1944, cxxvi, 73-79.

AN EVALUATION OF SULFONAMIDE MIXTURES AND VARIOUS ADJUVANTS FOR CONTROL OF SULFONAMIDE CRYSTALLURIA *

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RENAL complications due to sulfonamide therapy continue to be among the most frequent and serious attending the use of these drugs.^{1, 2, 3} Two main causes are established: (1) irritation due to formation in the kidneys or ureters of crystals largely of the acetylated drug and (2) nephrotoxic action. The causes of the latter are poorly understood. However, there is ample evidence to show that crystalluria is the result of the very low solubility of the acetylated drugs in urine that is acid in reaction.^{4, 5, 6, 7, 8} Despite numerous demonstrations of the effectiveness of alkalinization^{6, 9, 10, 11, 12} by means of sodium bicarbonate, lactate or citrate, many physicians either fail to employ alkalinization as a means of diminishing renal toxicity or use inadequate amounts to accomplish this result. Although the belief is widely held that administration of enough fluid to insure high urinary output is sufficient to overcome this hazard, our experience like that of others¹³ indicates that high urine volumes alone will not forestall sulfonamide precipitation, and that crystalluria is frequently observed in patients secreting large volumes of urine. If the hazard from this source is to be held to a minimum, additional measures are required.

A study of various means of decreasing or preventing renal irritation by sulfonamide crystals has been conducted coincidentally with other investigations of various sulfonamides in the Medical Wards of the Philadelphia General Hospital.† The study has included trial of sodium bicarbonate at several dosage levels. Additional information has been obtained concerning the critical pH of urine at which crystal-containing urines are divided from crystal-free urines and of the quantity of alkalinizing agent required to exceed the critical pH. We have had in mind also the fact that administering sodium salts in the required quantity has certain disadvantages and have studied the use of potassium bicarbonate, urea, ammonium chloride and sodium chloride for their effects on crystalluria.

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From the Committee on Chemotherapy and the Division of Biochemistry, Philadelphia General Hospital.

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A new approach to the problem has been offered by the work of Lehr^{14, 15} who proposed the use of mixtures of sulfonamides as a means of increasing total solubilities. He found that aqueous solutions saturated with sulfadiazine would dissolve appreciable additional quantities of another poorly soluble sulfonamide such as sulfathiazole or sulfamerazine. Thus if sulfadiazine and sulfamerazine are administered as mixtures containing equal parts of these drugs, the total amount of each excreted in the urine will be decreased and the concentrations in urine lowered, with diminished likelihood of crystal formation. A preliminary report on the behavior of sulfadiazine-sulfamerazine mixtures* with respect to crystal formation in urine is included in this paper.

PLAN OF THE INVESTIGATION

For the study of adjuvant drugs patients were assigned to the various treatment groups by a procedure designed to assure random selection. The cause of illness was pneumococcic pneumonia in about three-fourths and meningococcic meningitis in the remainder of the total number of patients. Our interest during the greater part of this study was mainly in sulfamerazine, and most of the patients studied, therefore, received this compound. The remainder received sulfadiazine or a mixture of sulfadiazine and sulfamerazine. Patients received 4 to 6 grams of drug daily. Further information concerning procedures used may be found in recent publications by the authors from this hospital. Alkalies or other agents intended to influence crystal formation were administered at the same time as the sulfonamides. All patients received sufficient fluid to maintain urinary output at the highest levels possible. An output of 3000 ml. was sought but in some seriously ill or markedly dehydrated patients this was not achieved.

The presence of crystals of acetylated sulfonamide derivatives in urine offers a practical indication of the solubility of these derivatives in the urine and of the potential hazard from intra-tubular or intra-ureteral concretum formation. Urine samples were collected between 7 a.m. and 2 p.m. An entire voiding was transferred to bottles and kept at 38° C. until examined. This was usually within an hour, although occasionally longer. Comparison of the specimens so collected with others examined immediately after being collected from the same patient showed close agreement with respect to occurrence of crystals, although an increase in count of crystals did occur in some specimens. Aliquots of 50 ml. were centrifuged, the sediment was suspended in 0.5 ml. of urine, and portions were examined in a counting chamber under the microscope. Counts were made of the number of crystals and red blood cells present. "Crystals" refers to the characteristic acetylated sulfonamide forms. Presence of crystals other than those of sulfonamides was disregarded. When the identity of the crystalline material present was uncertain, a portion of the sediment was washed and analyzed chemically.

* Sulfadiazine-sulfamerazine mixtures used in our studies were supplied as "Combisul-DM" by Dr. Norman L. Heminway, Schering Corporation, Bloomfield, New Jersey.

pH was determined by means of a glass electrode. Loss of carbon dioxide from the urine could not be prevented, and the measured pH thus was more alkaline than the actual pH of the urine in the bladder.

Red blood cells were so commonly detected by microscopic examination of urine from patients suffering from pneumonia or meningitis, both in the presence or absence of renal irritation by the sulfonamide administered, that their utility for detection of untoward effects of the sulfonamide was quite limited.

RESULTS

The incidence of sulfonamide crystals in urine in sulfadiazine treated patients of the control group was the same as that observed in patients receiving sulfamerazine under similar conditions (table 1).

TABLE I

Frequency of Crystalluria Due to Sulfonamides as Influenced by Various Agents
Relationship to Urine pH

Drug	Adjuvant		Crystalluria		Per cent	Urine pH		
	Type	Dose	Present	Absent		Av.	Low	High
		gm./day	Number of Specimens					
Sulfamerazine	None		41	114	26%	5.98	4.95	8.70
Sulfadiazine	None		17	46	28%	5.88		
Sulfamerazine	Sodium bicarbonate	6	14	45	24%	6.27	5.04	8.88
Sulfamerazine	Sodium bicarbonate	12	9	146	6%	7.14	5.16	9.23
Sulfamerazine	Sodium bicarbonate	24	3	97	3%	7.62	5.54	8.70
Sulfamerazine	Potassium bicarbonate	7.5	12	33	27%	5.98	5.08	7.55
Sulfamerazine	Potassium bicarbonate	15	10	32	24%	6.56	5.00	8.74
Sulfamerazine	Ammonium chloride	4	14	37	27%	5.59	4.87	7.33
Sulfadiazine	Sodium chloride	24	4	15	21%	5.71	4.98	7.13
Sulfamerazine	Urea	10	5	25	17%	5.93	5.02	8.60
Sulfadiazine	Urea	10	0	16	0%	6.08	5.44	7.04
Sulfadiazine-Sulfamerazine mixture	None		10	163	6%	—	—	—

When the urine pH was less than 7.15, about one specimen in four contained crystals of acetyl sulfamerazine (figure 1). When the pH was greater than 7.15, only one of 220 samples showed crystals of acetyl sulfamerazine. In this exceptional sample the pH was 7.57. Below pH 7.15, there was no correlation between pH and incidence or number of crystals per specimen.

Comparison of the groups receiving 6, 12, and 24 grams of sodium bicarbonate daily (table 1) shows that the incidence of crystalluria was unchanged from that of the control group when only 6 grams were administered. Twelve grams of sodium bicarbonate lowered the incidence of crystalluria to 6 per cent, as compared with a 23 per cent incidence in the group

receiving 6 grams. Twenty-four grams of sodium bicarbonate daily lowered the incidence of crystalluria to 3 per cent. This is not significantly different from the response of the 12 gram group when tested by the Chi square method, but the number of crystals per specimen was considerably lower when the higher dose was used.

The effect of the different dosages of sodium bicarbonate on urine pH is shown in figure 2 and explains clearly the ineffectiveness of the 6 gram doses.

Potassium bicarbonate was ineffective in both 7.5 and 15 gram dosages in reducing the incidence or number of crystals in urine (table 1). Figure 3 shows that potassium bicarbonate caused relatively little change in the urine pH; far less than that brought about by sodium bicarbonate in equivalent

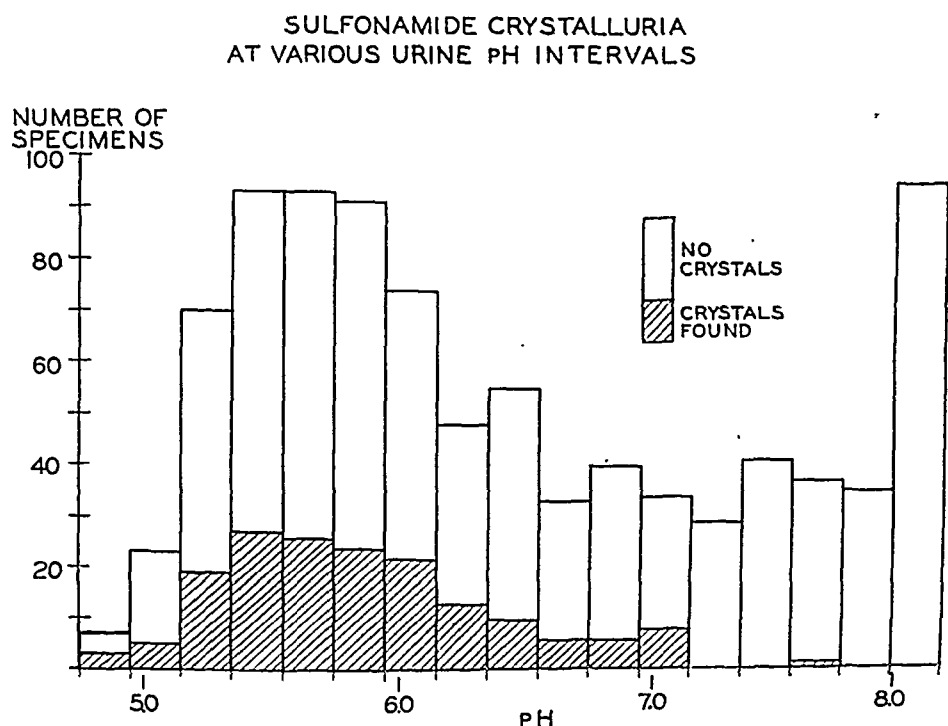


FIG. 1. Sulfonamide crystalluria at various urine pH intervals.

concentrations. Higher dosages of potassium salts were purposely avoided because of possible potassium retention with rise in concentration to levels causing depression of cardiac function in patients suffering from severe infections.

Ammonium chloride was used to learn whether further acidification of the urine would increase the frequency of crystalluria. However, the proportion of urines showing crystals was no greater than that of the patients of the control groups (table 1, figure 3).

Urea offers possibilities as an adjuvant to sulfonamide therapy, because of its action as a diuretic and because the solubility of the sulfonamides and of their acetyl derivatives is greater in urea solutions than in water.^{16, 17}

Table 1 shows that there is a somewhat lower incidence of crystal-containing urines in the urea treated group. Figure 3 shows that this effect was not due to change in urine pH. The number of individuals who could be studied was too small to permit conclusions to be made concerning its effectiveness.

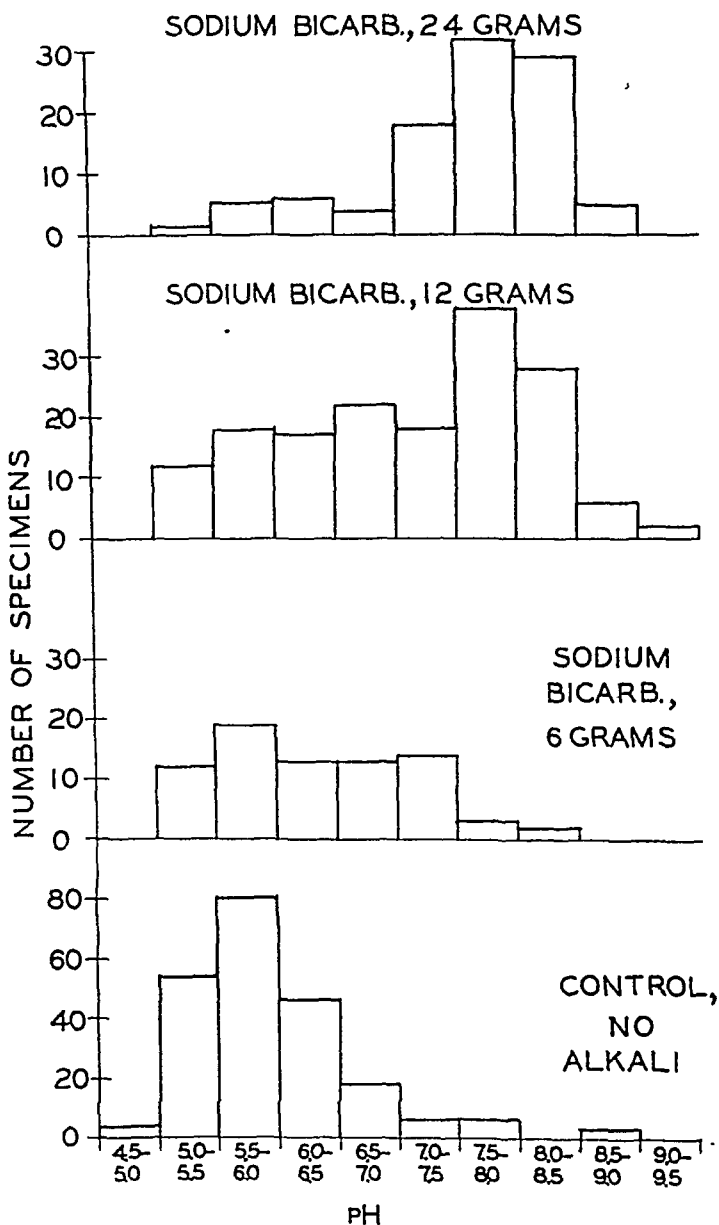


FIG. 2. Effect of sodium bicarbonate at several dosage levels on urine pH.

Further trial of urea is warranted, particularly since its use involves fewer hazards than does that of sodium or potassium salts.

The use of sodium chloride was suggested by the report of Lehr¹⁸ who found it to be effective in treatment of urinary tract complications due to

sulfonamides. Although the number of subjects here also is too small to permit conclusive evaluation, the incidence of crystal-containing urines appears to be unaltered (table 1).

The effect of sodium bicarbonate administration on concentration of sulfa-

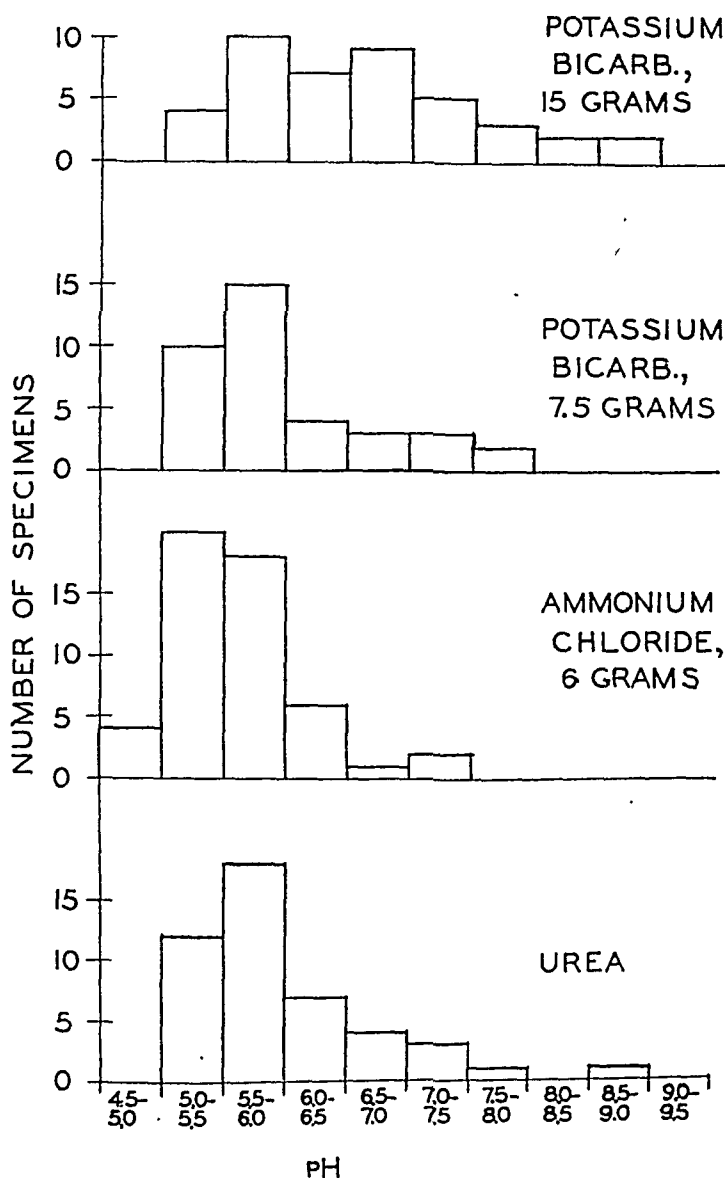


FIG. 3. Effect of potassium bicarbonate, ammonium chloride and urea on urine pH.

merazine in blood plasma is shown in table 2. Six grams of sodium bicarbonate daily is without effect, but 12 and 24 grams cause sufficient increase in excretion to lower the plasma concentration to an extent that is statistically and perhaps therapeutically significant.

TABLE II

Effect of Administration of Sodium or Potassium Bicarbonates on Concentration of Sulfamerazine in Plasma

Alkali	Dose	Number of Samples	Sulfamerazine Average Concentration
	gm./day		mg./100 c.c. plasma
None		70	13.4 \pm 6.9
Sodium bicarbonate	6	59	13.2 \pm 7.7
Sodium bicarbonate	12	73	11.5 \pm 6.5*
Sodium bicarbonate	24	112	10.6 \pm 4.9**
Potassium bicarbonate	7.5	65	12.1 \pm 5.2
Potassium bicarbonate	15	59	12.9 \pm 5.9

* Statistically significant difference.

** Highly significant difference.

COMBINED SULFONAMIDE THERAPY

Administration of sulfadiazine and sulfamerazine in mixtures containing equal parts of the two compounds resulted in a substantial decrease in the frequency with which crystals were found in urine compared with either drug alone (table 1). The total amount of drug given was the same, and concentrations in serum were comparable. Crystals were found in 6 per cent of the urine specimens when the sulfadiazine-sulfamerazine mixture was administered at the rate of four to six grams daily. The patients in this treatment group received no alkali or other adjuvant. Thus it may be seen that the

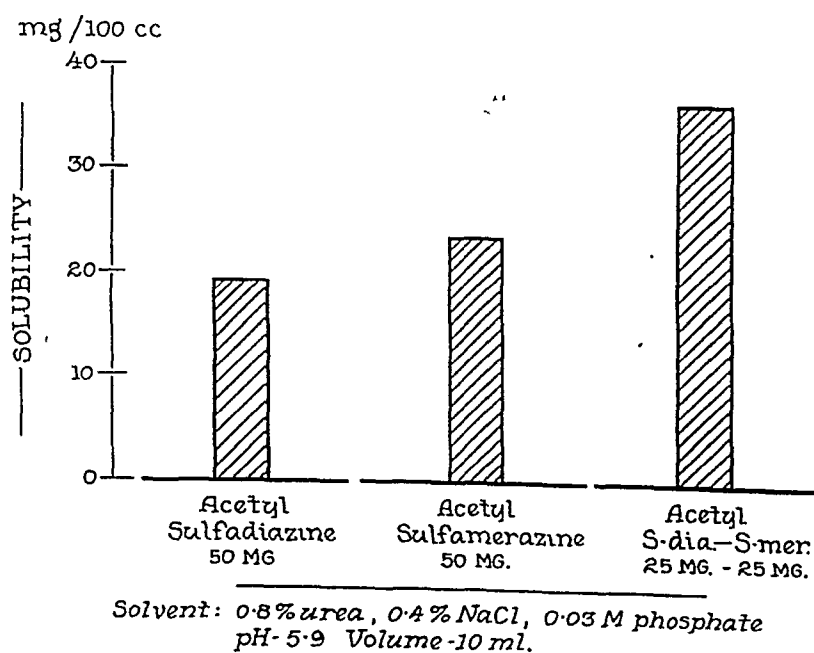


FIG. 4. Solubility of acetyl sulfadiazine and acetyl sulfamerazine singly and in mixtures.

incidence of crystals is the same as that in patients receiving either sulfadiazine or sulfamerazine alone when 12 grams of sodium bicarbonate were administered daily. However, a single patient of the 54 patients that have received sulfonamide mixtures showed gross hematuria associated with sulfonamide crystalluria. The therapeutic response to such a mixture in patients suffering from pneumococcic pneumonia and bacterial meningitis was satisfactory and will be the subject of a separate report.

Lehr's work on solubilities of sulfonamides in mixtures did not include studies of the acetylated derivatives. Since it is the latter that constitute the hazard of concrement formation, it seemed important to establish whether they would conform in their behavior to that of the sulfonamides themselves. Experiments devised for this purpose have shown that this is true and that the acetylated compounds also give higher total solubilities in mixtures (figure 4).

DISCUSSION

Formation of crystals and concretions of acetylated sulfadiazine and closely related sulfonamides is known to depend mainly upon (1) the concentration of the compound, (2) whether it is present in the form of acid or salt, and (3) concentration of urea and other constituents of urine having a solvent action. It is clear that the volume of urine secreted will determine (1) and (3) to a large extent and will also influence (2). Low volumes of urine will lead to high concentrations of the acetylated sulfonamides. At the same time proportionately less urea and other solvent substance will be present in the urine, since the acetylated sulfonamides are secreted by the tubules¹⁹ while the urea and associated substances are passively or actively reabsorbed. Concentrated urine also is more acid. The desirability of maintaining high urine outputs is acknowledged by all who have investigated the problem of sulfonamide concretions, yet it is at times difficult to maintain adequate urine volumes in seriously ill and febrile patients. Also, deposits of crystals may occur despite relatively high volumes of urine. Additional precautions thus are required. The solubility of the acetylated sulfonamides can be markedly increased by converting them to sodium salts. This conversion becomes appreciable at pH 7.0 and rises with great rapidity as the reaction becomes more alkaline. Concomitantly, crystals of these compounds disappear from the urine and the frequency of renal irritation decreases.

An alternative method, proposed by Lehr^{14, 15} avoids exceeding the critical concentrations at which crystallization will occur by using two or more sulfonamides simultaneously. Our preliminary observations indicate that this approach is as effective as the administration of sodium bicarbonate at the rate of 12 grams per day. The use of sulfonamide mixtures avoids certain disadvantages associated with the administration of sodium bicarbonate, namely the retention of sodium with or without alkalosis, and the lowering

of plasma concentrations of the sulfonamide consequent to administration of effective amounts of sodium bicarbonate.

Urea, investigated because of its combined action as diuretic and solvent, also offers promise. Again its use is especially advantageous when sodium salts should be avoided.

Potassium salts have been advocated^{20, 21} for use in such patients, but our data show them to be far less effective than sodium salts in equivalent amounts.

SUMMARY

1. The incidence of characteristic crystals of acetyl sulfonamide in urine was the same when patients received either sulfadiazine or sulfamerazine.

2. The critical pH of urine dividing crystal-containing from crystal-free samples was pH 7.15. Below pH 7.15, change in pH had no influence on occurrence of crystals.

3. Comparison of various amounts of sodium bicarbonate administered with the sulfonamide shows that at least 12 grams daily was required to lower the incidence of crystals substantially. Raising the bicarbonate intake to 24 grams daily was of doubtful benefit when all factors were considered.

4. Potassium bicarbonate was relatively ineffective when compared with sodium salts.

5. The response to urea as an adjuvant indicates that while less effective than sodium bicarbonate, its use may be beneficial.

6. A saturated solution of acetyl sulfadiazine will dissolve appreciable amounts of acetyl sulfamerazine. Thus the solubility of such a mixture is additive and exceeds that of either compound measured singly.

7. The use of sulfadiazine and sulfamerazine in mixtures containing equal parts of each drug led to a markedly decreased incidence of crystalluria compared with that observed when either compound was administered singly.

We wish to acknowledge the valued assistance of Miss Rita M. Fenwick, R.N. and her aids in the Fever Ward of the Philadelphia General Hospital.

BIBLIOGRAPHY

1. SIMON, M. A.: Pathologic lesions following the administration of sulfonamides, *Am. Jr. Med. Sci.*, 1943, ccv, 439.
2. SWARTZ, P.: Toxic effect of sulfonamide therapy on urinary tract, *Canad. Med. Assoc. Jr.*, 1944, 1, 440.
3. MURPHY, F. D.: Diseases of the kidney in *The cyclopedia of medicine and surgery-service*, 1945, F. A. Davis Co., Philadelphia, p. 320.
4. SUNDERMAN, F. W., PEPPER, D. S., and BENDITT, E.: Sulfathiazole in blood and urine, *Am. Jr. Med. Sci.*, 1940, cc, 790.
5. JENSEN, O. J., JR., and FOX, C. L., JR.: Hydrogen ion concentration and the solubility of sulfonamides in urine: the relation to renal precipitation, *Jr. Urol.*, 1943, xlix, 334.
6. GILLIGAN, D. R., GARB, S., WHEELER, C., and PLUMMER, N.: Adjuvant alkali therapy in the prevention of renal complication from sulfadiazine, *Jr. Am. Med. Assoc.*, 1943, cxxii, 1160.

7. WELCH, A. D., MATTIS, P. A., LATVEN, A. R., BENSON, W. M., and SHIELS, E. H.: Sulfamerazine (2-sulfanilamido-4-methylpyrimidine). 1. A comparison of sulfamerazine with sulfadiazine on the basis of absorption, excretion and toxicity, *Jr. Pharmacol. and Exper. Therap.*, 1943, lxxvii, 357.
8. BARNES, R. W., and KAWAICHI, K.: Factors influencing the formation of sulfonamide urinary concretions, *Jr. Urol.*, 1943, xlix, 324.
9. SCHWARTZ, L., FLIPPIN, H. F., REINHOLD, J. G., and DOMM, A. H.: The effect of alkali on crystalluria from sulfathiazole and sulfadiazine, *Jr. Am. Med. Assoc.*, 1941, cxvii, 514.
10. CLIMENKO, D. R., BARLOW, C. W., and WRIGHT, A. W.: Influence of sodium bicarbonate in preventing renal lesions from massive doses of sulfathiazole, *Arch. Path.*, 1941, xxxii, 889.
11. FOX, C. L., JR., JENSEN, O. J., JR., and MUDGE, B. H.: The prevention of renal obstruction during sulfadiazine therapy, *Jr. Am. Med. Assoc.*, 1943, cxxi, 1147.
12. GRIEP, A. H.: Note on alkalinization during sulfonamide therapy, *Univ. Hosp. Bull., Ann Arbor*, 1944, x, 44.
13. ROSENBLATT, P., and GRAYZEL, D. M.: Renal lesions in sulfonamide intoxication, *Urol. and Cutan. Rev.*, 1944, xlviii, 556.
14. LEHR, D.: Inhibition of drug precipitation in the urinary tract by the use of sulfonamide mixtures. I. Sulfathiazole-sulfadiazine mixture, *Proc. Soc. Exper. Biol. and Med.*, 1944, lviii, 11.
15. LEHR, D.: The prevention of renal complications by the therapeutic employment of sulfonamide mixtures. I. Sulfathiazole-sulfadiazine mixture, *Jr. Urol.*, 1946, lv, 548.
16. FEINSTONE, W. H., WILLIAMS, R. D., WOLFF, R. T., HUNTINGTON, E., and CROSSLEY, M. L.: The toxicity, absorption and chemotherapeutic activity of 2-sulfanilamido pyrimidine (sulfadiazine), *Bull. Johns Hopkins Hosp.*, 1940, lxvii, 427.
17. SOBIN, S. S., ARONBERG, L. M., and ROLNICK, H. C.: Nature of renal lesion with sulfonamides and its prevention with urea, *Am. Jr. Path.*, 1943, xix, 211.
18. LEHR, D.: Treatment of experimental renal obstruction from sulfadiazine. 1. Forcing of fluids and alkalinization, *Proc. Soc. Exper. Biol. and Med.*, 1944, lvi, 82.
19. REINHOLD, J. G., FLIPPIN, H. F., DOMM, A. H., ZIMMERMAN, J. J., and SCHWARTZ, L.: Renal clearances of sulfamerazine, sulfadiazine, sulfathiazole, and sulfapyridine in man, *Jr. Pharmacol. and Exper. Therap.*, 1945, lxxxiii, 279.
20. OHNYSKY, J., and WOLFSON, W. Q.: Potassium bicarbonate: An adjunct to chemotherapy in pneumonia complicating cardiac decompensation, *New England Jr. Med.*, 1944, ccxxxi, 381.
21. LAM, R. L.: Use of potassium bicarbonate as adjuvant alkali therapy with sulfonamides: Preliminary report, *Univ. Hosp. Bull., Ann Arbor*, 1944, x, 86.

IMMUNIZATION AGAINST INFLUENZA *

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DESPITE the fact that the greatest advances in knowledge of human influenza have been made since 1933, the name "influenza" invariably conjures up thoughts of 1918. Since the influenza viruses were not discovered ^{1, 2, 3} until more than a decade later, there can be no certainty regarding the relationship between the viruses known today and the 1918 episode. Nevertheless, it seems probable that the influenza viruses will be found to be causally related to future recurrences of the highly fatal disease. In comparing the pandemic of 1918 with subsequent epidemics, Francis ⁴ has remarked: "The differences enumerated appear to be those of degree—quantitative differences of broad epidemiologic rather than specific clinical or etiologic nature."

EPIDEMIOLOGIC VARIATIONS

For centuries pandemics of high mortality have constituted a recurrent threat to each generation. However, it should be emphasized that epidemics of a much milder disease are almost yearly occurrences. The epidemics of mild disease, known to be caused by Types A and B influenza virus, are characterized chiefly by a high degree of morbidity, but there also occurs a significant but variable increase in mortality. Since the discovery of the virus, epidemics of influenza A have occurred every two to three years, and it appears that the cycle for influenza B may be four to six years. Epidemics studied in the past 13 years have been due to one or the other of these viruses, but some year the independent cycles may coincide, resulting in a mixed epidemic. Simultaneous or successive infections by the A and B viruses in the same individual would, under these conditions, be possible. The consequences cannot be foreseen, since widespread occurrence of disease resulting from a combined infection by both viruses, or from a second attack by the virus of one type during the convalescent phase of infection by the other, is unknown, although occasional instances have been reported.

Apart from the widespread epidemics which call attention to the problem, it is now known that the disease occurs in localized outbreaks at times when generalized prevalence is not evident. Moreover, there have been repeated demonstrations of sporadic or isolated cases in the intervals between epidemics. Epidemiologically, then, influenza resembles other epidemic dis-

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eases in which man is the reservoir and in which the host-parasite relationship is in constant fluctuation.

CLINICAL VARIATIONS

Correlated clinical and laboratory investigations have revealed that wide variations exist in the clinical picture of influenza virus infections. As is the case with other recurrent infectious diseases for which immunity is short-lived, the clinical manifestations in the adult are modified by the residual immunity from previous exposures, while in children a more uniform picture is presented. Reference to a particular study⁵ illustrates this point in a young adult population. During the epidemic of influenza A in November and December 1943, observations were made in a group of approximately 900 unvaccinated men. In this group only 8 per cent were hospitalized with what might be called "typical" influenza. The criteria for hospitalization were based upon Army regulations requiring admission to hospital with temperatures of 100° F. or more recorded by mouth. By "typical" influenza is implied a temporarily incapacitating illness with abrupt onset, associated with fever, generalized aching and symptoms of respiratory tract irritation. An additional feature is the absence of gross evidence of pathologic lesions characteristic of infection by other etiologic agents. Although only 8 per cent exhibited illnesses of this degree, serologic study revealed that 40 per cent of individuals had been infected in the course of the epidemic. Further review indicated that in addition to the 8 per cent who were known to have had influenza A, 17 per cent experienced what would ordinarily be included under the nondescript terms of "a bad cold," "URI," or, to use the Army terminology, "mild nasopharyngitis," and the remaining 15 per cent appear to have had asymptomatic infections caused by the virus of influenza A.

In addition to being the cause of a mild disease, it is recognized too that the viruses of influenza A and B are sometimes associated with severe, fulminating disease reminiscent of the 1918 variety. Although a tendency has prevailed in some quarters to reserve the diagnosis of influenza for cases of this kind, it would appear from the illustration cited that it is in error to use the severe clinical types as the point of reference in considering the possibility of influenza as an etiologic diagnosis. These brief remarks are intended to indicate that the viruses of influenza, against which an immunizing agent is desired, contribute to the incidence of respiratory disease of man to a wider extent and with greater clinical variation than is generally recognized.

These comments serve to indicate the nature and the extent of the clinical as well as the epidemiologic problems which influenza presents.

IMMUNIZATION AGAINST THE EPIDEMIC DISEASE

It would not be possible in a paper of this kind to refer to all of the work on influenza that contributed to the advance of the problem to its present state. Many fundamental investigations, which should not pass unrecog-

nized, were made in the interval between the early and the recent studies on immunization against the epidemic disease. In the final analysis, the fundamental contributions were essential prerequisites for success.

Very early in the research on human influenza, an approach to the solution of the problem of control by methods of immunization was indicated. That a rise in antibody titer occurs following natural infection was demonstrated. It was soon discovered that similar changes could be induced artificially by subcutaneous injections of active or inactive virus, without the production of disease. A variety of vaccine preparations was conceived, employing virus contained in the lungs of ferrets or mice, in tissue culture, in the developing chick, and finally in the allantoic fluid of the embryo. With more information regarding the virus itself and with greater understanding of the quantitative relationship between virus dosage and immunizing effects knowledge was advanced. The desirability for extending to man the experimental observations made in animals was apparent. The use of human volunteers as a guide for the study of vaccinating procedures, the effectiveness of different preparations, and the practicability of different approaches furnished important preliminary information without awaiting the occurrence of natural epidemics.

Activities were accelerated by the War. Many investigators collaborated in their efforts under the Commission on Influenza of the Army Epidemiological Board to show that a practical means could be devised for controlling epidemics of influenza. The development of the vaccination studies of the Influenza Commission has been reviewed.⁶ A vast amount of information, both fundamental and applied, was obtained. The present discussion, however, will be limited to three practical questions: (1) the nature of influenza virus vaccines; (2) the degree of immunity engendered; and (3) the duration of immunity.

Nature of Influenza Virus Vaccines. The vaccine employed in the trials to be discussed consisted of a suspension of formalin-inactivated influenza viruses and contained representative strains of both types A and B. The culture medium for the virus was the chick embryo and the extra-embryonic fluids constituted the immediate source. Although these fluids are rich in virus, further concentration was deemed advisable in order to obviate the possibility of any failure that might be due to the use of insufficient antigen. Even though the precise dosage required was unknown, by concentrating the antigen it was hoped to compensate for the loss in immunizing potency for animals that accompanies virus inactivation. Two methods were devised for getting into a 1 ml. volume the quantity of virus contained in 10 ml. of extra-embryonic fluids of the developing chick. One method of concentration involves the collection of the precipitate formed when frozen allantoic fluid is allowed to thaw, and then resuspension of this precipitate, to which the virus is adherent, in one-tenth the original volume of the same fluid.^{7, 8} In the other method the virus is permitted to be adsorbed on the red cells of the embryo from which it is then released by a change in temperature into a volume of

physiological salt solution equivalent to one-tenth the original volume of harvested fluid.⁹ In the early studies of 1942–1943, vaccine prepared by both methods was employed. In the trials of vaccine by the Influenza Commission during the influenza A epidemic in 1943–1944, vaccine prepared by the red cell adsorption-elution method was used.

In these investigations a single injection of 1 ml. was given. A second inoculation seems to afford no further benefit in terms of antibody level. The booster effect noted with other immunizing agents is not observed with influenza virus. The side effects or reactions accompanying the use of influenza vaccine will be mentioned later.

Degree of Immunity. During the epidemic of influenza A that occurred throughout the United States in the winter of 1943–1944, 12,500 ASTP students were involved in studies conducted uniformly but independently by members of the Commission on Influenza in six investigating groups in different parts of the country.¹⁰ In each study,^{9, 11-15, 5} alternate individuals in a company received the virus vaccine, or were given a control inoculation. The accumulated statistics¹⁰ indicated that 7.1 per cent of unvaccinated and 2.2 per cent of vaccinated individuals were hospitalized with "typical" influenza. Expressed in another way, 3.2 times as many control persons became ill as did those vaccinated; or 76 per cent of all cases occurred in that 50 per cent of the population that was unvaccinated. A further statement describing the result has been that a 75 per cent reduction in attack rate occurred, or that the vaccine was only 75 per cent effective.¹⁶ Although at first glance this may seem to be a fair statement of the efficacy of vaccination, there are certain essential factors that require consideration for a critical evaluation of these data.⁵ It is important to point out that in a study of the prophylactic effect of a vaccine against an epidemic disease that is transmitted from man to man, special consideration must be given to the controls for the following reasons. If the untreated individuals are interspersed with vaccinated persons in the same population and if the vaccine has any effect, the controls are no longer untreated since their opportunity for exposure necessary to contract disease is reduced, to say nothing of the quantitative aspects of exposure which probably determine severity. Thus, under such circumstances, the controls are not true controls since they are at a reduced risk when compared with the population at large. If, on the other hand, two populations are compared, one vaccinated and the other unvaccinated, the latter could then be considered a truly untreated group. However, there might then be some doubt as to whether chance played a rôle, or whether the epidemic would have struck with equal force if vaccination had not been done.

To return, then, to the estimate that vaccination was 75 per cent effective, this seems to assume that the attack rate in the control half of the populations under study was not influenced by the presence of vaccinated persons, but was the expected rate had vaccination not been done. Two observations which have a bearing on this point suggest that the assumption may be incorrect. (1) At the University of Minnesota¹¹ the attack rate among 1206 individuals

in the study group, half of which had received influenza vaccine, was 5.9 per cent. This rate was "considerably lower than in certain other groups on the campus, in one of which an attack rate of 38 per cent was observed among approximately 500 men, who were living under conditions similar to those of the vaccinated groups." (2) At the University of Michigan,⁵ where the over-all incidence was 5.4 per cent in the study group, again one-half of which was vaccinated, an incidence of 20 per cent was observed in a company of unvaccinated men. These data are more to the point when it is recognized that in the two institutions the incidence of disease in the unvaccinated controls was 9.06 per cent and 8.58 per cent, respectively, as compared with the 38 per cent and 20 per cent in other comparable units in which no vaccination had been done. These observations strongly suggest that the incidence of illness recorded in the controls was influenced by the presence of an equal number of vaccinated persons and that the effectiveness of vaccination probably greatly exceeds that described by a comparison of vaccinated and controls in this study.

Certain of the investigators¹⁴ have suggested that an epidemic involving a higher attack rate would discriminate less between vaccinated and control populations than does a disease of low rate, and that vaccination would be less effective if incidence rates were 20 to 30 per cent. Again, this assumes that the 7 per cent attack rate represents the true rate without influence of vaccination. That this assumption is open to question has just been indicated. In direct refutation, however, is the situation observed at the University of Michigan⁵ where in the analysis of results a division was made in terms of residence, since it appeared that a much higher attack rate was observed in one group as compared with another. The higher rates were observed in those companies quartered in a large dormitory, while a much lower incidence occurred in a group of similar size dispersed in 11 fraternity houses. In the dormitory group of 824 men, an incidence of 13.39 per cent was observed in the unvaccinated half of the population as compared to 2.66 per cent in the vaccinated; whereas in the companies comprising 607 men in the 11 fraternity houses, the incidence in the controls was 4.65 as compared with 1.31 in those vaccinated. Contrary to speculations cited earlier, it would appear that a higher attack rate would enhance rather than diminish the difference between vaccinated and controls by affecting a relatively greater proportion of unvaccinated than vaccinated persons. A similar conclusion is suggested by an analysis of the antibody levels in vaccinated versus unvaccinated groups, in relation to the apparent reduction in susceptibility in individuals with higher antibody titers.⁵

Earlier in this paper mention was made of the fact that in the course of an epidemic of influenza the infections were manifested clinically in various forms, from the asymptomatic variety to the moderately severe disease. In the discussion thus far, incidence of disease, or attack rates, have expressed the amount of hospitalized illness arbitrarily called "typical" influenza. This is not a good term, but it expresses the idea. In the study at the University

of Michigan, all cases of respiratory disease occurring among the ASTP students were considered, including those cases that ordinarily do not come to the attention of physicians in private practice. It was of considerable interest that in this group of cases, the majority of which were afebrile or had oral temperatures of less than 100° , there was no difference in incidence between controls and vaccinated when a diagnosis of "localized infection of the respiratory tract" or "common cold" was made. However, when the diagnosis was "mild" influenza, a distinct difference between controls and vaccinated was evident, although the difference was much less than observed in terms of the more severe illness similarly diagnosed. Serological study showed that about 90 per cent of cases hospitalized because of severity were influenza A, while in the dispensary group about 65 per cent were caused by the type A virus. Inclusion of non-influenza cases in the latter category would tend to reduce the difference between controls and vaccinated; however, it is also believed that in many instances vaccination simply reduced the severity of illness and some who might have had "typical" influenza developed the milder disease that did not result in incapacitation.

Duration of Immunity Following Vaccination. The general opinion has been that the duration of effectiveness of influenza vaccination is rather short. It has been variously stated as being a matter of weeks or months. By and large such statements have been based on questionable evidence or have been made without due consideration of all of the factors involved. From recently reported studies, both *indirect* and *direct* evidence is available to support the contention that the duration of effectiveness of influenza vaccination is considerably longer than a few months, when vaccine of suitable potency is employed.

The *indirect* evidence is as follows: From studies conducted by Hirst, Plummer and Friedewald¹¹ in New York and Hale and McKee¹² in Iowa during the epidemic of influenza A in 1943-1944, it was learned that prior to the seventh day following inoculation, no difference in incidence of illness occurred in vaccinated and control subjects. Thus, it seems that approximately a week is required for the development of the immunizing effect. This phenomenon appears to coincide with the development of a demonstrable increase in specific antibody in the serum. It might be expected, therefore, that the degree of persistence of the increased antibody titer resulting from vaccination might reflect the duration of immunity, just as the appearance of serum antibody parallels the onset of immunity. This possibility becomes more plausible when it is considered that in a comparison of vaccinated and unvaccinated individuals who had corresponding levels of serum antibody, the probability of contracting influenza was of the same order.⁵ It should be borne in mind that the antibody titers in the unvaccinated subjects must represent the residual effect from a previous natural exposure which occurred, very probably, not more recently than three years before. The apparent identity in significance between antibody produced by natural infection and antibody stimulated artificially by vaccination strengthens the hypothesis

that the measure of persistence of the increased antibody titer following vaccination may indicate the degree of persistence of immunity.

With this in mind let us examine the information available on the question of the rate of decline in antibody titers elevated by vaccination. Studies were undertaken during the winter of 1942-1943¹⁷ to test the efficacy of vaccination, using the same vaccine preparation referred to earlier; that is, one in which virus was concentrated approximately ten-fold by adsorption from the allantoic fluid onto the red cells of the embryo and subsequent elution. The anticipated epidemic did not occur until a year later. In the interim, however, antibody titers were determined in vaccinated persons at intervals up to the onset of the epidemic one year after vaccination. The findings were rather surprising in view of previous reports that the increased antibody titer following vaccination was fleeting and that the duration of immunity was brief. With respect to the serologic results, they revealed that mean antibody titers declined gradually from the two-week maximum, but were still well above the prevaccination level at the end of 12 months. What is perhaps more significant, however, is the fact that, despite the general decline, the distribution of individual titers was still considerably above that observed before vaccination. The data need not be repeated here since they appear elsewhere. Until it becomes possible to define the exact significance of the various antibody levels in terms of immunity, one can only comment that, in the majority, the level of antibody at the end of one year was beyond the zone of greatest susceptibility. Thus, if level of antibody parallels the state of susceptibility, then the effectiveness of the vaccine employed is sufficient for at least one season, and perhaps longer.

This is supported by *direct* evidence gathered during the epidemic that occurred one year after the vaccination study was begun.¹⁷ Although the intention was to compare the incidence of influenza among the alternately vaccinated and control individuals in each of the institution wards under study, this was not possible because of the low incidence and sporadic occurrence of disease in these groups. Fortunately, however, a sufficient number of wards was excluded from the immunization studies, and it was among these that sharp outbreaks occurred. It was therefore possible to compare the incidence of influenza in so-called "vaccinated" and "unvaccinated" wards. Striking differences were observed. There were 1319 persons residing on the 15 "unvaccinated" wards, and the incidence of influenza in this group was 12.4 per cent; whereas among the 1916 persons residing on the 20 "partially vaccinated" wards, the incidence of influenza was only 1.9 per cent. When considered in terms of the individual wards, it was found that the highest attack rate occurring among the "unvaccinated" wards was 29.1 per cent; whereas among the "partially vaccinated" wards the highest rate was 6.5 per cent. Eight of the 15 "unvaccinated" wards experienced incidence above 10.0 per cent, whereas none of the "partially vaccinated" wards had rates exceeding 6.5 per cent, and all but four had rates below 4.4 per cent.

It would appear from these data, in terms of comparable segregated vac-

cinated and unvaccinated populations rather than in terms of vaccinated and unvaccinated individuals, that vaccination had a significant effect for as long as a year at least. To some extent this parallels the observations made in nature—that epidemics of influenza A do not recur at intervals of less than two years. It may be that the mass immunizing effect of the epidemic takes that long to decline.

Reactions Accompanying the Administration of Vaccine. Reactions to influenza vaccine correspond in severity and character to reactions following typhoid vaccine. They are primarily attributable to the virus content.¹⁸ In the studies referred to,^{5, 11-15} approximately half of the vaccinated individuals had some complaints and about 1 to 2 per cent developed febrile reactions up to 101.5° F. within 24 hours of inoculation. Such symptoms usually last no longer than a day. At the site of inoculation, edema, redness and tenderness may develop in about 12 hours and persist for about a day or slightly longer. The local and systemic symptoms are related to the quantity of virus administered rather than to any non-virus impurities that are present.

One word of caution is warranted, and that is the danger of anaphylactic reactions in persons with *known* egg-sensitivity, who are given any vaccine of egg origin. The development of sensitivity to repeated inoculations seems to be less of a risk or no risk at all. An adult who has once been given an injection of vaccine originating from an egg, and this includes a good number of vaccines, is much less likely to have an acute reaction than one who is to have his first inoculation.

With respect to age variations, influenza vaccines of the degree of concentration spoken of here are practically untried in any significant series of children. The indications at present are that it must be used with care, and systemic reactions suggest that smaller dosages may be advisable.

DISCUSSION

On the basis of the results of these studies carried out by the Commission on Influenza, the Surgeon General directed that plans be made to vaccinate the entire Army in the fall of 1945, using vaccine prepared in the same manner as that employed in the field studies. For the first time development of mass production as well as mass immunization with influenza vaccine was involved and was accomplished successfully.

In November and December 1945, a widespread epidemic of influenza B occurred. The program of vaccination of the Army provided the extraordinary opportunity for observing its effect on a large scale. Through a combination of circumstances at two universities^{19, 20} it was possible to make careful comparisons between fully vaccinated groups of Army students and comparable groups of unvaccinated individuals. Under these conditions the ratio of cases, vaccinated versus unvaccinated, was 1 to 9. At one of the universities the incidence of hospital admissions for respiratory disease was 1.1 per cent among 600 vaccinated men, whereas among the 1100 unvaccinated

men it was 9.9 per cent. Moreover, infections of mild degree occurred in a high proportion of the unvaccinated group and almost not at all in the vaccinated group. Although it might be said that the vaccinated group escaped the epidemic by chance, it should be pointed out that results at both institutions were consistent and that these observations reflected the general trend in the vaccinated Army as compared with other comparable groups where vaccination had not been employed.

In view of certain impressions which have been created, one can comment that neither the results nor the program adopted by the Army was dependent upon the preparation of vaccine by Sharples' centrifugation. Little or no centrifuged vaccine was used in the Army vaccination program of 1945. Actually, the centrifugation studies to which this refers²¹ did not come to light until after the results of the successful field trials against influenza A had been achieved. Evidence obtained thus far does not support the a priori contention that the more highly purified vaccine produces fewer reactions nor that it is a more effective antigen.

Although incontrovertible evidence is now available that the resistance of man to infection by the viruses of influenza A and B can be enhanced, it is also evident that the problem of controlling epidemics of influenza by means of immunization cannot be approached only from the viewpoint of affording individual protection. It is clear that the individual influences the mass effect, and that the mass effect influences the individual response. The problems of the future are to devise means for enhancing^{22, 23} and prolonging individual protection and to extend our present knowledge into the field for the purpose of establishing the minimum requirements for preventing the epidemic phenomenon. When the latter has been accomplished, it may be found that the requirements for individual protection need not be as rigid as is assumed at present. Until such time, it would appear advisable to suggest that the protection of individuals should be practiced.

BIBLIOGRAPHY

1. SHOPE, R. E.: Swine influenza, *Jr. Exper. Med.*, 1931, liv, 349.
2. SMITH, W., ANDREWES, C. H., and LAIDLAW, P. P.: Virus obtained from influenza patients, *Lancet*, 1933, ii, 66.
3. FRANCIS, T., JR.: A new type of virus from epidemic influenza, *Science*, 1940, xcii, 405.
4. FRANCIS, T., JR.: Epidemiology of influenza, *Jr. Am. Med. Assoc.*, 1943, cxxii, 4.
5. SALK, J. E., MENKE, W. J., JR., and FRANCIS, T., JR.: A clinical epidemiological and immunological evaluation of vaccination against epidemic influenza, *Am. Jr. Hyg.*, 1945, xlii, 57.
6. FRANCIS, T., JR.: The development of the 1943 vaccination study of the Commission on Influenza, *Am. Jr. Hyg.*, 1945, xlii, 1.
7. HIRST, G. K., RICKARD, E. R., and WHITMAN, L.: A new method for concentrating influenza virus from allantoic fluid, *Proc. Soc. Exper. Biol. and Med.*, 1942, 1, 129.
8. HARE, R., McCLELLAND, L., and MORGAN, J.: A method for the concentration of influenza virus, *Canadian Jr. Pub. Health*, 1942, xxxiii, 325.
9. FRANCIS, T., JR., and SALK, J. E.: A simplified procedure for the concentration and purification of influenza virus, *Science*, 1942, xcvi, 499.

10. Members of the Commission on Influenza, Army Epidemiological Board: A clinical evaluation of vaccination against epidemic influenza. Preliminary report, *Jr. Am. Med. Assoc.*, 1944, cxxiv, 982.
11. RICKARD, E. R., THIGPEN, M., and CROWLEY, J. H.: Vaccination against influenza at the University of Minnesota, *Am. Jr. Hyg.*, 1945, xlii, 12.
12. HALE, WM. H., and MCKEE, A. P.: The value of influenza vaccination when done at the beginning of an epidemic, *Am. Jr. Hyg.*, 1945, xlii, 21.
13. EATON, M. D., and MEKLEJOHN, G.: Vaccination against influenza: A study in California during the epidemic of 1943-44, *Am. Jr. Hyg.*, 1945, xlii, 28.
14. HIRST, G. K., PLUMMER, N., and FRIEDEWALD, W. F.: Human immunity following vaccination with formalized influenza virus, *Am. Jr. Hyg.*, 1945, xlii, 45.
15. MAGILL, T. P., PLUMMER, N., SMILLIE, W. G., and SUGG, J. Y.: An evaluation of vaccination against influenza, *Am. Jr. Hyg.*, 1945, xlii, 94.
16. HIRST, G. K., RICKARD, E. R., and FRIEDEWALD, W. F.: Studies in human immunization against influenza. Duration of immunity induced by inactive virus, *Jr. Exper. Med.*, 1944, lxxx, 265.
17. SALK, J. E., PEARSON, H. E., BROWN, P. N., SMYTH, C. J., and FRANCIS, T., JR.: Immunization against influenza with observations during an epidemic of influenza A one year after vaccination, *Am. Jr. Hyg.*, 1945, xlii, 307.
18. Studies to be published.
19. FRANCIS, T., JR., SALK, J. E., and BRACE, W. M.: Effect of vaccination against epidemic influenza B, *Jr. Am. Med. Assoc.*, 1946, cxxxi, 275.
20. HIRST, G. K.: Personal communication.
21. STANLEY, W. M.: The preparation and properties of influenza virus vaccine, concentrated and purified by differential centrifugation, *Jr. Exper. Med.*, 1945, lxxxi, 193.
STANLEY, W. M.: Biochemical studies on influenza virus, *Chem. and Eng. News*, 1946, xxiv, 755.
STANLEY, W. M.: The efficiency of different Sharples centrifuge bowls in the concentration of tobacco mosaic and influenza viruses, *Jr. Immunol.*, 1946, liii, 179.
22. FRIEDEWALD, W. F.: Enhancement of the immunizing capacity of influenza virus vaccines with adjuvants, *Science*, 1944, xcix, 453.
23. SALK, J. E.: The immunizing effect of calcium phosphate adsorbed influenza virus, *Science*, 1945, ci, 122.

HEPATIC INSUFFICIENCY. I. PATHOPHYSIOLOGY AND CLINICAL ASPECTS *

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EXPOSURE to exotic diseases and infectious hepatitis of members of the armed forces necessitates reevaluation of concepts of hepatic insufficiency by physicians. Recognition of relative hepatic insufficiency is not on a par with the diagnosis of insufficiency in other organs, and many physicians do not concern themselves with the liver until overt jaundice appears. Sensitive biochemical methods reveal that impaired liver function is far more common than previously suspected. The immense recuperative power of the liver masks the insufficiency until the parenchyma fails to eliminate bilirubin.

Mass wartime experience has firmly established the clinical and biochemical attributes of hepatic insufficiency in cases of hepatitis.¹⁻⁸ The similarity of biochemical, clinical and pathologic data in icteric and non-icteric phases of the disease has given impetus to the recognition of hitherto unrecognized forms of hepatic failure. Clinical endeavor has long been directed to the detection of concealed liver disease. Now thousands recovered from infectious hepatitis form a fruitful group of subjects to study the aftermath of this disease in relation to the development of hepatic insufficiency.

The quest for a single miracle test of liver function disturbance is now fully recognized as futile. The need for the use of a combination of suitable tests for assessment of hepatic failure is appreciated. Random choice of a battery of tests may also fail of this purpose. A careful selection of tests is indicated. A fixed group of tests may be recommended for general screening purposes. The proper selection of tests for investigative and clinical problems depends on the *type* and *stage* of hepatic insufficiency. The uses and limitations of the tests are determined by these factors. Specific physiologic defects determine the clinical aspects of liver failure. The stages of progressive failure must also be recognized. The proper selection of the laboratory tests is guided by the clinical evaluation of the symptoms and signs of liver failure in terms of type of pathophysiology and grade of liver insufficiency. These phases of the subject are developed in the following material. The methods of clinical diagnosis and the principles of treatment of liver insufficiency will be presented at a later date.

THE CLINICAL ATTRIBUTES OF HEPATIC INSUFFICIENCY

THE symptoms and signs of hepatic insufficiency are often vague and correspond to those of many systemic diseases. In many instances they are

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secondary effects upon the liver. For example, a large share of digestive complaints present in heart failure are referable to impaired hepatic circulation, and liver disturbance may develop with menstruation, anesthesia, coryza, thyrotoxicosis, malaria, infectious mononucleosis, pneumococcus infections, trench foot, amebiasis, burns treated with tannic acid, and after sulfonamide therapy.

The clinical picture of hepatic insufficiency is found in publications dealing with fatty liver,⁹ infectious hepatitis, subacute diffuse liver necrosis.¹⁰ The clinical aspects of the compensated and decompensated stages of cirrhosis¹¹ contribute further to the picture of liver failure. Pre-icteric symptoms are present in 50 to 90 per cent of subjects with hepatitis and liver atrophy. Large numbers of cases of toxic and infectious hepatitis, however, go undetected because jaundice never develops or remains subclinical. Hepatic insufficiency is studied to advantage in this type of clinical material. Great dependence is placed on biochemical determinations to gauge the state of activity of the latent disease process.

The symptoms and signs encountered in pre- and post-icteric forms of hepatitis are representative of other forms of hepatic insufficiency. Profound anorexia, nausea and vomiting occur. Constipation and diarrhea are the rule, normal bowel movements exceptional. Epigastric distress, when present, is aggravated by exertion; a sudden jog or motion induces a sharp pain that radiates backward to the lumbar region. Most patients complain of great fatigability, mental depression, and low-grade bifrontal headache. A layman will describe the individual as being lazy and tired. There is disproportionate dyspnea on slight exertion. Each outbreak of hepatitis seems to be characterized by some distinctive features. In one group that followed vaccination, fatigue, depression, anemia and dermatitis were common. Some epidemics were marked by prodromal chills, fever and lymphadenopathy. Hepatomegaly varied in incidence. Some observers stressed normal size of spleen and liver. Itching was present in 5 per cent of cases during the pre-icteric phase in one group. Neurological complications have been emphasized in reports.^{12, 13}

The symptomatology of *latent* liver disease often resembles that of chronic exhaustive states, so that a diagnosis of psychoneurosis^{3, 6} is often entertained until jaundice appears. Patients who attempt physical activity find themselves unequal to the task. Jaundice may become apparent for the first time, reappear, or become accentuated. In military service the symptoms of masked subsiding hepatitis were labeled as neurasthenia, and individuals bearing them were credited with seeking easy assignments. Fatigue, exposure, emotional stress or actual trauma precipitated manifest jaundice, disclosing the latent hepatic insufficiency. It was most likely persistence of the disease, rather than a recurrence.

The absence or subsidence of jaundice may lead to clinical misconceptions. Although jaundice is important in focusing attention on the liver, its disappearance must not be assumed to mark cessation of liver damage. It is

difficult to determine the abatement of hepatitis without laboratory aids. Although hepatitis subsides rapidly in most individuals, a low-grade process may persist for months or years in some. Jaundice may reappear periodically during periods of physical or emotional distress. In about 0.2 to 0.5 per cent of cases, depending on the severity of the epidemic, hepatitis goes on to acute hepatic necrosis. It has been estimated in different series that 6 to 32 per cent of cases of cirrhosis result from infectious hepatitis with slow progression of the lesion. The recital of the latency and progression of the liver disease in significant numbers of individuals emphasizes the importance of recognition of hepatic insufficiency as a major clinical task.

Despite the varied symptomatology of hepatic insufficiency several clinical patterns are delineated. Jaundice and hepatosplenomegaly are common features. The associated symptom-complexes fall into at least five categories:

1. A clinical picture simulating a generalized infection, 'grippal' in nature, with its recovery phase of post-grippal asthenia. The presence of chills may arouse suspicion of cholangitis.

2. An enteric form in which gastrointestinal disturbances predominate. Anorexia, distaste for food, epigastric discomfort and intestinal motility disturbances are the chief complaints.

3. Neurologic-neuropsychiatric forms, marked by meningeal irritation, peripheral nerve disease, neuromuscular, neurocirculatory, and psycho-neurotic complaints.

4. A nutritional deficiency state, evidenced by anemia, malnutrition, tendency to bleeding into the skin and from mucous membranes, weakness, sub-*vitaminosis*.

5. Cases marked by the clinical manifestations of portal failure: ascites, gastrointestinal bleeding, and dilated venous collaterals.

APPLIED PHYSIOLOGY

Unfortunately, there is no single index or test to gauge the competency of the liver. Study of hepatic insufficiency by biochemical and pathologic correlation, however, suggests four general considerations:

1. Reduction in efficiency is not symmetric: one or more functions can be severely impaired and others remain normal.

2. Hepatic insufficiency can exist without demonstrable histologic changes.

3. Hepatic reserve allows destruction of a major fraction of the cells without evidence of insufficiency. But relatively *minor* damage, involving *all* the cells, impairs functional efficiency.

4. Clinically, therefore, the symptoms of hepatic insufficiency may persist, long after the last biochemical evidence of impaired function can be demonstrated. Hepatosplenomegaly may, in turn, persist long after both the symptoms and impaired function are no longer apparent.

THE TYPES OF FUNCTIONAL FAILURE

Study of changes in hepatic function involves consideration of three elements: The *first* is a defect in the parenchymal cell itself. The *second* is a vascular defect that limits portal and arterial flow; and the *third* element is the failure of biliary drainage. Fulminating disease in the parenchymal cell may result in necrobiosis, while vascular insufficiency tends to produce atrophy.

Acute yellow atrophy is, in reality, acute, diffuse necrosis with loss of cellular units. The shrinking of liver size, following portal failure, readily results from atrophy of parenchymal units, nourished principally by unmixed portal blood. Prolonged disease of the parenchymal cells with the resulting change in architecture is usually followed by vascular failure. Thus, one finds combined defects where the disease is of long standing.

The metabolic functions of the liver are usually considered from the viewpoint of the foodstuff acted upon—namely: carbohydrate, protein, or fat, and not from the viewpoint of the mechanism of the function. The functions result from a chain of interrelated reactions. A single type of cell performs innumerable functions. Efficiency is secured by reducing the number of enzyme systems to a minimum. The so-called detoxication mechanism of the liver is not necessarily purposeful. The liver does not have a fixed formula ready for every new chemical presented to the body. Substances arriving through the portal circulation are treated in accordance with their chemical resemblance to physiologic substances. The liver acts as a barrier against toxic products formed in the intestine. Substances may be conjugated or oxidized. There is a common exchange of mechanisms for handling substances.

Many of the so-called toxic substances exert a deleterious action mainly by virtue of the fact that they resemble a nutrient and exclude that nutrient from being utilized by the cell. Furthermore, such antimetabolites may occupy a strategic crossroad, so to speak, and blockade a number of functions which utilize a key enzyme system.¹¹ Because of this the liver may be deficient in some functions, yet show normal efficiency otherwise.

1. *Hepatic Insufficiency of Parenchymatous Origin.* Congenital defects may provide situations which contribute to our knowledge of metabolic mechanisms. Cases have been reported of individuals who have inborn deficiencies that result in impairment of isolated liver functions. Von Gierke described a condition in which there was an unusual accumulation of glycogen in the liver. Most recent evidence suggests that it is due to an intracellular disturbance of the phosphorylase-phosphatase system which balances the synthesis and disintegration of glycogen in the liver. In another rare disease, chronic hypergalactosemia, the liver is unable to convert galactose to glycogen. The resulting galactosuria, hepatosplenomegaly, anemia, and albuminuria are diminished or lost when lactose and galactose are withheld

The presence of excess galactose in the blood inhibits glycogenolysis and produces hypoglycemia.

A condition in which there is an inborn defect in the excretion of bilirubin by the hepatic cells has been described as a constitutional hepatic dysfunction or familial hyperbilirubinemia.¹⁵ Except for the periodic episodes of jaundice which these patients demonstrate, there has been no evidence of progression of the disease.

2. *Hepatic Insufficiency Resulting from Circulatory Changes in the Liver.* It has been pointed out that, in addition to the inherent functional efficiency of the parenchymal cell, the ultimate work performed is conditioned by the competency of the hepatic vascular elements and biliary passages. The relation of the double afferent blood supply to the hepatic architecture and the portion of the lobule nourished by portal vein and both portal vein and hepatic artery in the normal and diseased liver have been the subject of extensive study. Although the function of the hepatic cell itself is important in acute hepatitis and acute necrosis, with the development of cirrhosis in the more chronic forms of liver disease, the threat from the vascular lesion becomes preëminent. The prognostic significance of reduction of portal flow was accented by Mann's demonstration of the need of portal flow as a stimulus for regeneration.¹⁶ Failure of the portal circulation, with portal hypertension, causes prehepatic deviation of nutrients into the caval circulatory system. The resulting nutritional deficiency produces secondary liver atrophy, comparable to that resulting from an Eck fistula. The hepatic cells become increasingly dependent on the blood from the hepatic artery, thus losing the *reciprocal* control of portal flow. Loss of this sluice mechanism changes conditions so that the parenchymal cell functions continuously instead of intermittently. When the lesion progresses and impedes hepatic artery flow, irreversible parenchymal failure obtains.

3. *Hepatic Insufficiency of Bile Duct Origin.** The metabolism of the bile pigments and their relation to hepatic insufficiency will not be discussed here. The defect lies in the liver cell or the channels leading bile from the liver. Resorbed stercobilin also enters into consideration in the problem of liver insufficiency.

THE GRADES OF FUNCTIONAL FAILURE

It would be convenient if a solitary function was the first to be sacrificed in hepatic failure. But experience gained in the laboratory and clinic disclaims uniformity in the first function to lose efficiency as the liver becomes insufficient. The next best approach is to group the functions with reference to the order in which they are lost as the liver becomes progressively insufficient. The first group includes those functions which are ¹⁸ affected when the damage is *minor*; the second when it is *intermediate*; the third when the damage is *marked*. In this third group functional deficiency is detectable

* The rôle played by the Kupffer-stellate system in the pathogenesis or clinical aspects of hepatic insufficiency is important but awaits clarification.

only after marked damage is present; changes in this group are of especial prognostic significance. The arrangement, however, is subject to modification by the mechanism underlying the production of the insufficiency. Obstruction of the biliary tract, porto-caval shunt, bacterial or viral damage to the hepatic cell, functional overload, or blockade of the enzyme system may modify certain groups of functions. Attempts to differentiate intrahepatic and obstructive jaundice by tests are limited in value because establishment of biliary obstruction for any length of time usually produces hepatic cell dysfunction, yielding dissociated results.

I. *The Functions Modified in Relatively Minor Hepatic Insufficiency* (table 1 A).

1. The production of *bile salts* is among the early functions disturbed in liver cell injury. It is important to determine the cholic, desoxycholic, and conjugated forms, separately. The functions of synthesis, reclamation, conjugation and destruction all affect the level of excretion in the bile and urine and the blood level. There is evidence of production of abnormal types of bile salts in disease conditions.

2. Glucuronic acid production is diminished early in hepatic insufficiency. Alcohols, ketones, alkaloids and phenols are conjugated with glucuronic acid in the liver.

3. The ease of the determination of bilirubin in body fluids and the alteration of its solubility, diffusibility and reactivity after action by the liver have encouraged extensive study of this substance. Because of the hepatic

TABLE I

The Grades of Hepatic Insufficiency

A. Liver Dysfunction in *Minor* Grade Insufficiency

Bile salt synthesis
Glucuronic acid production and synthesis
Detoxication mechanisms; organic substances
Glycine synthesis
Glycogen synthesis and storage
Plasma protein synthesis; electrophoresis changes
Bilirubin excretion
Bromosulfothalein excretion

B. Liver Dysfunction in *Moderate* Grade Insufficiency

Blood cholesterol; total and ester fraction
Prothrombin-vitamin K response
Alkaline phosphatase blood level
Carotene-vitamin A synthesis, storage
Thiamin-niacin metabolism
Water metabolism
Blood glucose homeostasis
Estrogen inactivation
Lipid mobilization and metabolism
Iron-copper storage and utilization

C. Liver Dysfunction in *Severe* Grade Insufficiency

Deamination of amino acids
Glycogenolysis-neoglucogenesis
Ketone body formation
Electrolyte imbalance
Blood volume control; pulmonary edema.

reserve, the ability to excrete an overload of bilirubin injected intravenously becomes impaired before an increase in the blood level is clinically manifest. Hence early diminished function can be demonstrated by the bilirubin tolerance test. The production of bilirubin is a function of the reticulo-endothelial system, and while the Kupffer cells participate in this, the parenchymal cell is involved in its excretion. Isolated excessive production of bilirubin theoretically does not produce jaundice, but, in clinical experience, hepatic damage soon ensues and clinical icterus results. This development of hepatic insufficiency with excessive bilirubin excretion explains the clinical limitations of the van den Bergh test, as compared with the theoretical considerations underlying this procedure.

4. The ability of the liver to excrete foreign dyes and pigments is also diminished early in hepatic insufficiency. Here again the presence of biliary obstruction will alter the interpretation of modified excretion. A variety of dyes are used by roentgenologists in visualization of the gall-bladder. The dye is administered by mouth, excreted by the bile, and concentrated in the gall-bladder. It is assumed that there is no hepatic insufficiency when a non-functioning gall-bladder is reported.

5. The so-called detoxication of some substances by the liver is diminished early in hepatic insufficiency. When cinchophen is administered by mouth, a portion is excreted in the urine as an intermediary oxidation product known as oxycinchophen. When the liver is insufficient the portion excreted as oxycinchophen increases. The ease of measuring the oxycinchophen and the fact that it is an intermediary step in the detoxication of cinchophen recommend this test.

6. The liver performs many functions essential in the protein economy. Although the exact mechanism of the storage of protein by the liver is not known, it is known that it is one of the functions that may be lost early in hepatic damage. There have been no reports of the injurious effect of excessive storage of protein in the liver, such as have been described for fat and glycogen. The rôle of the liver in the synthesis of the plasma proteins has been the subject of extensive study. The site of albumin synthesis has not been established, but there is no doubt that the major fraction is derived in the liver. The relative concentrations of the various protein constituents of plasma change early in hepatic insufficiency. Although these cannot be determined biochemically until the stage of insufficiency has progressed, sensitive physical methods such as electrophoresis reveal the early changes. These account in part for the applicability of various non-specific tests such as the Takata-Ara, cephalin-cholesterol flocculation, Weltmann coagulation, colloidal gold, and thymol turbidity reactions as tests of liver dysfunction.

7. The rate of synthesis of glycine is diminished early in hepatic insufficiency. This may be tested by determining the rate of conjugation of the glycine with benzoic acid as indicated by the excretion of hippuric acid. After oral ingestion of sodium benzoate one must take into account its rate and completeness of absorption, the availability of glycine for conjugation,

and the ability of the kidney to excrete the hippuric acid formed. Studies in which sodium benzoate and an excess of glycine have been injected intravenously have indicated that it is the synthesis of the glycine that is the limiting factor and not the rate of conjugation. Furthermore, a fraction of the benzoate is conjugated with glucuronic acid and excreted in the urine. Because of alternate pathways of conjugation, conclusions drawn from the excessive excretion of hippuric acid are subject to criticism. Although the kidney of normal individuals can excrete hippuric acid at two to three times the rate necessary, interpretation in individuals with damaged kidneys is hazardous.

8. The ability to store glycogen is diminished as hepatic insufficiency develops, but this is not easily measured. The function that can be estimated is the rate at which the various sugars are utilized or converted to glycogen. If one wished to name them in order of the ease with which they are converted to glycogen, levulose would be first, then glucose, and galactose last. D-lactate is converted to glycogen with greater ease than the sugars. The normal amount of lactate produced by metabolic processes can be utilized easily in minor hepatic insufficiency, and the blood lactate level does not rise. To show that there is a diminution of the ability of the liver to utilize lactate, a larger amount must be injected intravenously. When there is advanced liver damage the blood lactate does rise without a test with an overload. There are so many factors in the utilization of glucose that one would have to use tagged glucose to determine its utilization.

II. *Intermediate Group of Functions—Those Which Are Impaired as Liver Injury Progresses* (table 1 B).

1. When hepatic insufficiency is present the *cholesterol* and *cholesterol ester* content of the blood is diminished. However, in some varieties of toxic hepatitis and in the regenerative phase of hepatitis they may be elevated. In the present state of our knowledge, explanations of the lipid levels in the blood in hepatic disease follow circumstantial reasoning. Marked elevation of all the lipids of the blood is encountered in cases with long-standing stricture of the common duct, in which there is also marked liver damage.

2. Damage to the parenchymal cell is marked by inability to utilize vitamin K. In biliary obstruction, vitamin K may not be absorbed because of the lack of bile, and a diminished synthesis of prothrombin may result. When the parenchymal cell is damaged, the liver cannot synthesize prothrombin, even in the presence of adequate intake of vitamin K. The mechanism by which vitamin K regulates the synthesis of prothrombin is not known.

3. The serum alkaline phosphatase is elevated in obstructive jaundice, and it is normal or slightly elevated in parenchymal injury. However, in some cases of toxic hepatitis, such as follow arsphenamine administration, there is a marked elevation of the phosphatase. It is known that phosphatase is excreted in the bile and that there is a slight rise in the blood phosphatase after hepatectomy in dogs. The actual rôle of the parenchymal cell in phosphatase regulation is not known. Histochemical study of sections

of liver tissue shows a decrease in the phosphatase activity during hepatic necrosis. The activity is increased after starvation or protein depletion.

4. In hepatic insufficiency there is a reduction in the conversion of carotene to vitamin A. The vitamin A is stored in the Kupffer cells of the liver. Hence, when the liver is insufficient, the blood level of vitamin A may be low, the tolerance curve flat, and the dark adaptation reduced. In liver damage, limitation of the storage of vitamin C and thiamin has been noted.

5. The liver is involved in the regulation of water balance, and a defect in the ability to excrete added water by way of the kidney is noted in patients having hepatic insufficiency.

6. The part played by the liver in the regulation of the blood sugar is disturbed in hepatic insufficiency. In some cases there is hypoglycemia and a flat glucose tolerance curve, whereas in others there is a diabetic picture. It will be recalled that when synthalin was used in the treatment of diabetes, it was found that the reduction of blood sugar was the result of damage to the liver. Hyperglycemia and an elevated glucose tolerance curve are sometimes seen in hepatic insufficiency, simulating diabetes. If injury to the hepatic cells continues, hypoglycemia results.

7. There is a diminished destruction of estrogens in hepatic insufficiency. This probably accounts for the gynecomastia and testicular atrophy that is sometimes noted in cirrhosis of the liver.¹⁸ Normal male patients will excrete about 10 per cent of an intramuscular dose of estrogen, whereas male patients suffering from cirrhosis of the liver may excrete up to 80 per cent of the injected quantity. It has been suggested that the liver also inactivates progesterone.

8. In some instances the injured liver loses its ability to discharge its fat, and although the lipotropic substances—choline, methionine, and lipocaic—aid in the prevention of fat deposition, they may fail to influence the injured liver laden with fat.

III. *Functions Which Are Modified When Hepatic Insufficiency Is Marked* (table 1 C).

These functions are fundamental to survival and are preserved as long as possible. Studies of the functions that are impaired early in hepatic damage are applicable in vivo; the functions that are impaired after marked damage can be studied in liver slices and isolated, perfused livers. It will also be observed that the latter functions are more fundamentally inherent in the cell and older phylogenetically.

1. Amino acids are deaminated in the liver with insignificant amounts deaminated in the kidney and intestinal musculature. Since the ammonia that is split off is not utilized, it is combined with carbon dioxide in the liver to form urea. In man, urea synthesis is limited to the liver. Both of these functions are impaired when hepatic insufficiency is advanced. The amino acid content of the blood may be elevated and the urea content diminished in advanced cirrhosis or acute liver atrophy. The tyrosine, found in the liver during liver autolysis, has been attributed partly to failure of deamination,

TABLE II

The Pathophysiology of the Common Symptoms and Signs of Hepatic Insufficiency

Clinical Symptom, Sign	Parenchymal Failure	Vascular Defect	Biliary Failure, Stasis
A. Primary Parenchymal Defect			
Anorexia	+	—	—
Fatigability	+	—	—
Myasthenia	+	—	—
Myalgia	+	—	—
Arthralgia			
Dyspnea	+	—	—
Constipation	+	—	—
Diarrhea			
Acneform rash	+	—	—
Anemia	+	—	—
Fetor hepaticus	+	—	—
Hepatic Coma	+	—	—
Mental Depression	+	—	—
Plasma Protein Changes	+	—	—
Hypoproteinemia			
Hyperglobulinemia			
Electrophoresis			
Pattern Changes			
Ceph.-Chol. Flocculation			
Reaction			
Colloidal Gold			
Thymol Turbidity			
B. Primary Vascular, Circulatory, Hemodynamic Defect			
Splenomegaly	—	+	—
Ascites	—	+	—
Venous Collaterals	—	+	—
Caput Medusae			
Esophageal Varices			
Hemorrhoids			
Venous Bruit	—	+	—
Epigastrium			
Hematemesis	—	+	—
C. Primary Biliary Stasis or Failure			
Xanthelasma	—	—	+
Pruritus	—	—	+
Nyctalopia	—	—	+
Osteomalacia	—	—	+
Osteoporosis			
Constipation	—	—	+
Diarrhea			
Steatorrhea	—	—	+
Bleeding tendency	—	—	+

TABLE II—*Continued*

Clinical Symptom, Sign	Parenchymal Failure	Vascular Defect	Biliary Failure, Stasis
<i>D. Parenchymal-Vascular Defects</i>			
Spider Angiomata	+	+	—
Edema			
Generalized }	+	+	—
Pulmonary }			
Hypervolemia	+	+	—
Hypoproteinemia	+	+	—
<i>E. Parenchymal-Biliary Defects</i>			
Jaundice	+	—	+
Steatorrhea	+	—	+
Epigastric }	+	—	+
Distress }			
Pruritus	+	—	+
'Cholemia'	+	—	+
Bleeding Tendency }	+	—	+
Hypoprothrombinemia }			

but mainly to autolysis of hepatic tissue. Intravenous injection of tyrosine or casein hydrolysate in suitable amounts, when deamination is inefficient, is followed by amino acid retention in the blood. The specific dynamic action of protein digestion is reduced *late* in liver injury. By the same reaction employed in converting the ammonia derived from deamination, the liver filters out the ammonia formed in the intestine and converts it to urea. Elevation of the blood ammonia in cirrhosis of the liver is disproportionate to the degree of failure of urea synthesis, because some ammonia passes by the liver via the porto-caval shunt.

2. The conversion of glycogen to glucose by the liver persists even in severe liver injury. Except in von Gierke's disease, amylase activity continues in the liver even after death. The hypoglycemia of terminal phases of liver disease is due to glycogen poverty.

3. The ability to oxidize fatty acids to ketones is not altered until late in hepatic insufficiency.

4. The regulation of electrolyte balance by the liver is disturbed in advanced liver disease. Similarly the part it plays in fluid balance is diminished. The factors that are changed in ascites and edema associated with liver disease are not fully defined.

5. The part played by the liver in the control of blood volume is altered in advanced liver disease.

THE CLINICAL ASPECTS OF FUNCTIONAL DEFECTS

One functional defect, or two types of defects, may combine and produce the symptoms and signs of liver failure. The common symptoms and signs of liver disease have been correlated with the physiologic defects from which they likely arise (tables 2 a, 2 b, 2 c, 2 d, 2 e).

SUMMARY

Wartime experience with infectious hepatitis has increased the significance of liver disease in clinical practice. The fact has been brought home that jaundice is merely one easily visible sign of liver disease. Serious forms of liver damage occur without overt jaundice. Early recognition and suitable treatment of hepatic insufficiency favor remission of the disease process. Relapses readily occur and lingering forms of hepatitis have been reported.

The symptoms and signs of liver insufficiency have been reviewed and classified.

Hepatic insufficiency, unfortunately, cannot be detected by a single test or procedure. The need for more elaborate measures is recognized. To meet this, pathophysiologic disturbances have been analyzed with an eye to bringing the laboratory procedures into closer agreement with the common clinical symptoms and signs of liver failure.

The fundamental types of physiologic defects underlying hepatic insufficiency have been enumerated. The functions of the liver have been graded according to progressively increasing degrees of failure—namely: *minor*, *moderate*, *severe*.

The symptoms and signs of liver disease have been tabulated according to their pathophysiologic mechanisms.

The ready clinical recognition of hepatic insufficiency is rapidly approaching realization. Tests and procedures for the detection and estimation of the various types and stages of hepatic insufficiency are available, and appropriate selection is guided by the knowledge of individual types of physiologic defects, the grades of liver failure and their connections with the common symptoms and signs of liver disease.

BIBLIOGRAPHY

1. BARKER, M. H., CAPPS, R. B., and ALLEN, F. W.: Acute infectious hepatitis, Jr. Am. Med. Assoc., 1945, cxxviii, 997-1003.
2. FINKS, R. H., and BLUMBERG, R. W.: Epidemic hepatitis with and without jaundice, Arch. Int. Med., 1945, lxxvi, 102-113.
3. POLLOCK, M. R.: Pre-icteric stage of infective hepatitis, Lancet, 1945, ii, 626.
4. RENNIE, J. B.: Infective hepatitis with special reference to prognosis, Am. Jr. Med. Sci., 1945, ccx, 18-29.
5. BENJAMIN, J. E., and HOYT, R. C.: Disability following postvaccinal (yellow fever) hepatitis, Jr. Am. Med. Assoc., 1945, cxxviii, 319-324.
6. CARAVATI, C. M.: Posthepatitis syndrome, South. Med. Jr., 1944, xxxvii, 251.
7. BARKER, M. H., CAPPS, R. B., and ALLEN, F. W.: Chronic hepatitis in the Mediterranean theatre, Jr. Am. Med. Assoc., 1945, cxxix, 653.

8. SNELL, A. M., WOOD, D. A., and MEINENBERG, J.: Infectious hepatitis with especial reference to its occurrence in wounded men, *Gastroenterology*, 1945, v, 241.
9. KEEFER, C. S., and FRIES, E. D.: The fatty liver, its diagnosis and clinical course, *Trans. Assoc. Am. Phys.*, 1942, lvii, 283.
10. LAWRENCE, J. STEWART: Subacute necrosis of the liver without icterus, *Lancet*, 1946, ii, 41.
11. SNELL, A. M.: Clinical aspects of portal cirrhosis, *Ann. Int. Med.*, 1931, v, 338.
12. STOKES, J. F., OWEN, J. R., and HOLMES, E. G.: Neurological complications of infective hepatitis, *Brit. Med. Jr.*, 1945, i, 477.
13. BYRNE, E. A. J., and TAYLOR, G. F.: An outbreak of jaundice with signs in the nervous system, *Brit. Med. Jr.*, 1945, i, 477.
14. WOOLEY, D. W.: Some new aspects of the relationship of chemical structure to biological activity, *Science*, 1944, c, 579-583.
15. COMFORT, M. W., and HOYNE, R. M.: Constitutional hepatic dysfunction: clinical study of 35 cases, *Gastroenterology*, 1944, iii, 155-162.
16. MANN, F. C.: I. Studies in the dehepatized animal. II. Restoration and pathologic reactions of the liver, *Jr. Mt. Sinai Hosp.*, 1944, xi, 1-22, 65-73.
17. WACHSTEIN, MAX: Influence of dietary deficiencies and various poisons on the histochemical distribution of phosphatase in the liver, *Arch. Path.*, 1945, xl, 57-67.
18. GLASS, S. J., EDMONDSON, H. A., and SOLL, S. N.: Excretion of estrogen after the injection of estradiol and estrone into men with cirrhosis of the liver, *Jr. Clin. Endocrinol.*, 1944, iv, 54-57.

COLORADO TICK FEVER*

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INTRODUCTION

IN 1930 Becker¹ described a disease he called Colorado tick fever, which up to that time had been assumed to be a mild form of Rocky Mountain spotted fever. The only experimental basis for this differentiation was that he could not obtain symptoms nor the typical scrotal reaction of Rocky Mountain spotted fever in guinea pigs following inoculation of blood from these cases. In 1940 Topping, Cullyford and Davis² undertook a systematic study of Colorado tick fever. They found it to be apparently associated with the bite of the wood tick, *Dermacentor andersoni* Stiles as postulated by Becker, but did not prove this. Neither were they able to transmit the disease to animals nor determine the etiological agent. Their studies convinced them that Colorado tick fever was of frequent occurrence in Colorado. It has also been reported in other Western states.

CLINICAL

The individual with Colorado tick fever has always been in a tick infested area four to six days before the onset of symptoms. Usually a tick is found attached to the body. Prodromata are lacking as the disease has a sudden onset ushered in by chilly sensations. Generalized aching of the entire body with headache, deep ocular pain and lumbar backache are the prominent symptoms. Photophobia, anorexia, nausea and sometimes vomiting are a part of the syndrome. With the onset of symptoms, the temperature begins to rise, reaching its height of between 102 to 104° F. within 24 hours. There is a concurrent increase in the pulse rate. This attack lasts approximately two days to be followed by a symptom free phase of like duration. The temperature is usually subnormal during the remission. The second attack is like the first but may last a day longer. Either attack may be more severe than the other. Although this is the usual pattern, the attacks and remission may vary from one to four days. Single and triple attacks have been recorded, but these are rare. Physical examination reveals only a mild erythema and slight conjunctival injection. There is no exanthem. Complications or deaths have never been recorded. Treatment is symptomatic. For several days following the disappearance of symptoms, the individual may feel weak and tired, but is usually able to resume normal activities.

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The significant laboratory findings are limited to the leukocytes. Typically the white blood cell count falls to between 2,000 and 3,000 cells per cubic millimeter, the lowest count being reached during the second attack. All types of the white blood cells are reduced in absolute numbers with the exception of the monocytes. There is a shift to the left in the granulocytes. The band forms may outnumber the segmented cells when the count is lowest. The white blood cell picture gradually returns to normal in four to seven days following clinical recovery.

Figures 1, 2 and 3 show the significant findings in three cases of this disease.

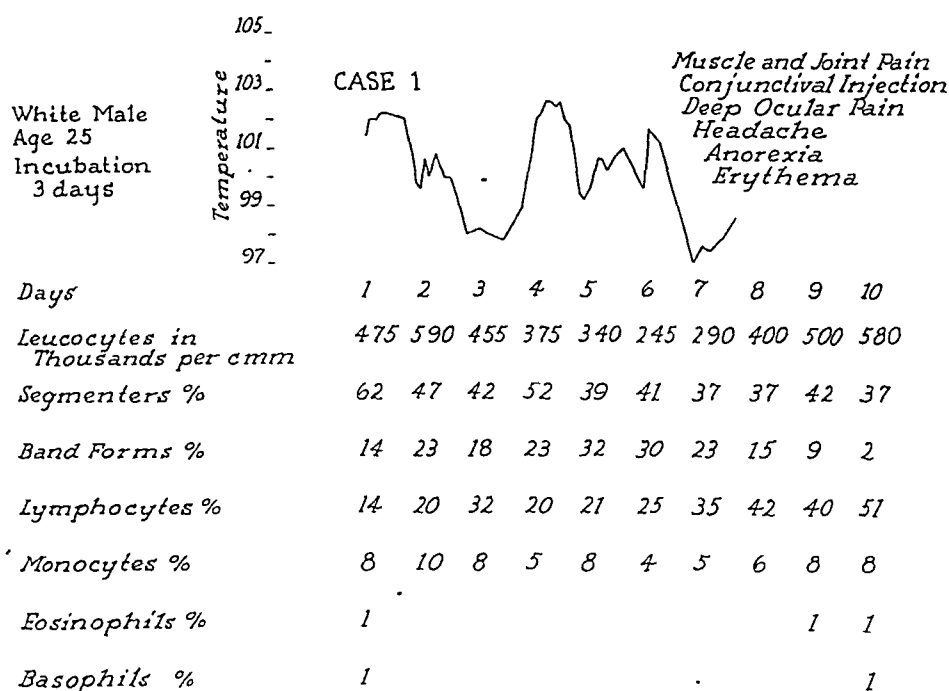


FIG. 1. Colorado tick fever in an experimental subject.

A STATEMENT OF THE PROBLEMS

Although Becker and others were convinced that Colorado tick fever is a distinct disease entity, the fact that it is probably transmitted by the same vector as Rocky Mountain spotted fever caused the feeling to persist that it is a mild form of this disease. Because of its striking clinical and hematological similarity to dengue, certain investigators suggested the possibility that Colorado tick fever is tick-borne dengue. Before the question of these relationships could be settled, it was necessary to determine where the infectious agent might be found. It would then also be possible to make further studies as to immunity, transmission to an experimental animal, etiology and the mode of spread.

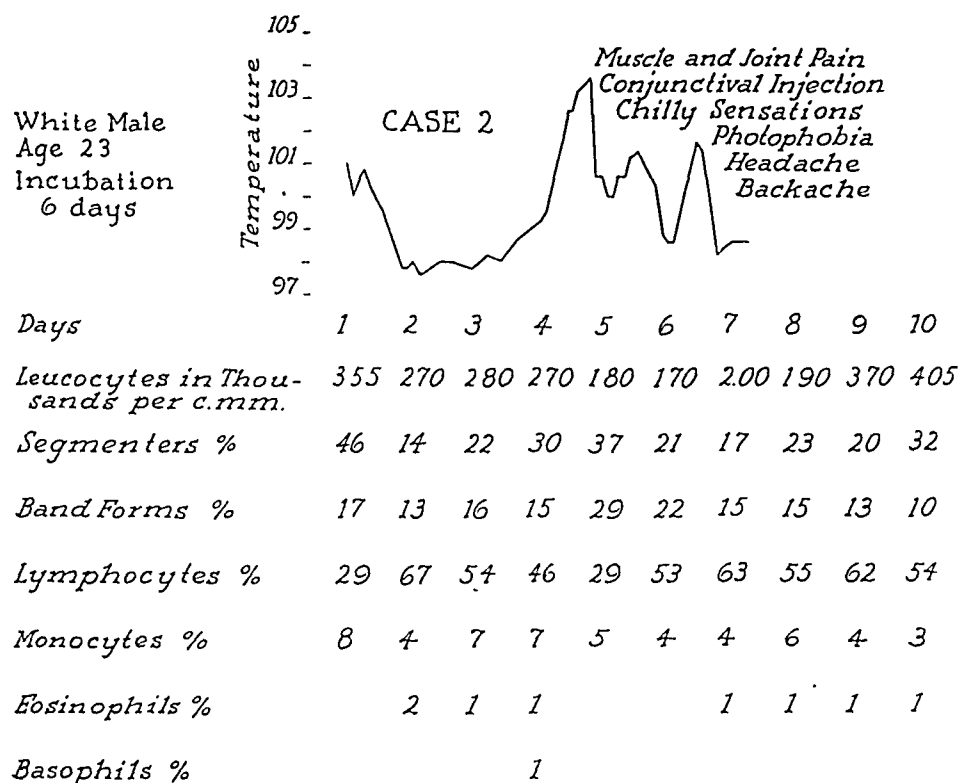


FIG. 2. A naturally acquired case of Colorado tick fever.

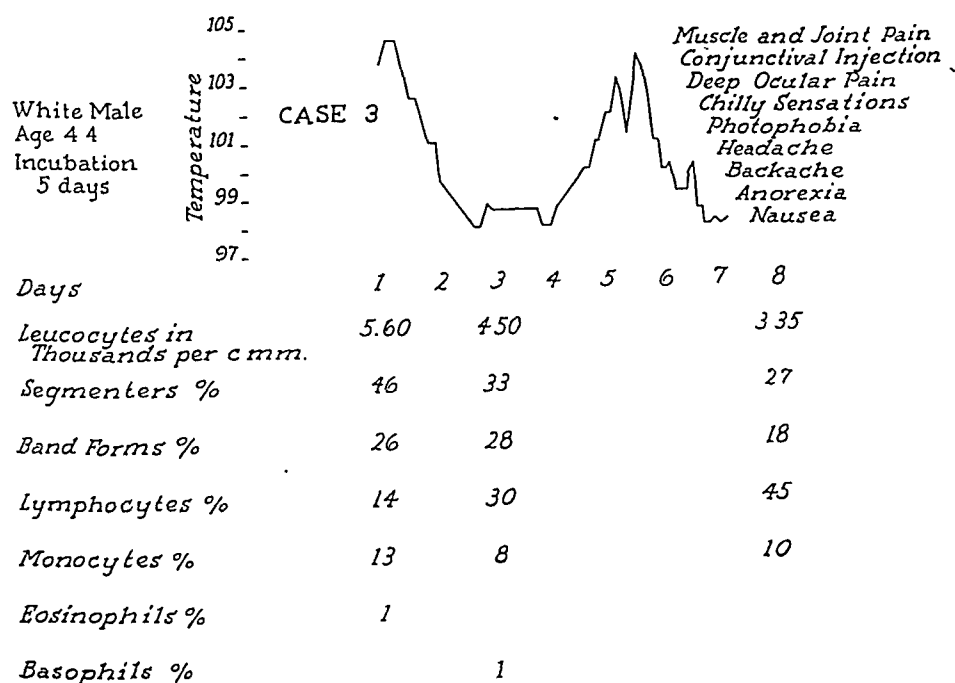


FIG. 3. A naturally acquired case of Colorado tick fever.

EXPERIMENTAL RESULTS

Human volunteers were used in an attempt to find the infectious agent. Sera taken from natural instances of the disease during the first or second attack caused typical Colorado tick fever when injected subcutaneously into these volunteers. A later experiment also proved the agent to be present in the blood during the remission.⁴ Successive human to human transfers, the longest being a series of six, did not seem to increase or decrease the virulence of the disease although the incubation period was usually three instead of four to six days. It was during this phase of the work that the changes in the differential distribution of the white blood cells were first noted, a fact previously unrecorded.

There are no reports of an individual having the disease a second time. In order to test the immunity, three of the original volunteers were reinoculated with a different strain of the infectious agent nine to 12 months after the original infection. They did not develop the disease, indicating that Colorado tick fever confers at least a short immunity.⁵ Several volunteers could not be infected. These individuals had lived in endemic areas for many years.

To test the assumption that Colorado tick fever is a mild manifestation of Rocky Mountain spotted fever, human volunteers were immunized against Rocky Mountain spotted fever with four instead of the recommended two doses of tick vaccine.³ One month following the last dose, these vaccinated volunteers were inoculated with Colorado tick fever serum. The disease they developed was indistinguishable from naturally acquired Colorado tick fever. One of the natural cases we studied had been immunized against Rocky Mountain spotted fever three months before acquiring Colorado tick fever.⁴ Two individuals who had had both diseases have also been brought to our attention⁵; another is reported by Shaffer.⁶ Finally the fact that later work proved that Colorado tick fever is not a rickettsial infection confirms Becker's assumption that the disease is not a mild form of Rocky Mountain spotted fever.

Since clinically and hematologically Colorado tick fever and dengue are strikingly similar, their possible relationship remained to be elucidated. As both diseases confer at least a short immunity to themselves, each should protect against the other if they are identical. Six human subjects were inoculated with dengue and developed typical disease. Two were later reinoculated and found immune. The remaining four were injected with the infectious agent of Colorado tick fever. All developed typical disease with the exception of one individual who had previously lived in an endemic area. One volunteer was first inoculated with Colorado tick fever and later with dengue. He developed both diseases. These experiments seem to indicate that Colorado tick fever and dengue are distinct diseases.⁷

In order to make possible a wider latitude in the continuation of the

experimental work than was permitted by the use of volunteers, it was decided to attempt the infection of an experimental animal. We found the golden hamster (*Cricetus auratus*) to be susceptible. Evidence of infection was adduced by the finding that the white blood cell count is definitely lowered as it is in man, although there is no characteristic change in the differential count in these animals.⁸ It was first necessary, however, to establish the normal blood cell values for the golden hamster. This was done on a series of 114 normal animals in which the white blood cell count was $8,088 \pm 1,773$ ⁸ as compared to $4,540 \pm 1,777$ in a group of 65 infected animals. As further proof of the successful infection of the hamster, serum from the seventh hamster transfer was also inoculated into a volunteer who developed typical Colorado tick fever.

In the early serial transfers of the infectious agent, the hamsters appeared normal, but beyond the twelfth passage, the animals began to die and a mortality of 25 to 50 per cent was common.⁴

Histologic studies of the tissues of infected animals revealed that the spleen was the only organ that showed variations from the normal. There were alterations in the cellular type and arrangement of the follicular lymphoid tissue as well as a partial or complete disappearance of the normal well defined follicular margin. Normal hamster serum carried through successive groups of animals failed to elicit these responses. The splenic reaction was first observed on the second day following inoculation, reached its height on the third day and continued through the fifth day.⁹ This reaction occurred in approximately 80 per cent of a series of 522 infected hamsters and is more consistently found after the strain has been adapted to the animals by several passages.

Having infected the hamster, it was now possible to proceed to a determination of the etiology of Colorado tick fever. All attempts at visualization of the organism had failed. It could not be grown on any of the common laboratory media nor on chick embryo.^{2, 4} It was logical to assume that the agent was a virus, and therefore filtration experiments were tried with gradacol membranes of known porosity. The agent was found to pass a 24 m μ membrane, although two passages were usually required in hamsters in order to elicit the typical white blood cell response. Such filtrates did not infect man. However, these same filtrates did cause characteristic human disease if they were first passed through hamsters.¹⁰

In order to obviate the possibility that hamster serum per se or some agent picked up from the serial passage of hamster serum might cause symptoms in man and hamsters similar to Colorado tick fever, the following experiment was done using animals selected at random from our colony. The serum of five normal animals was pooled and injected into 10 hamsters and this process repeated serially through 10 groups of approximately 10 animals each. The white blood cell counts and the splenic reactions in this series of animals were normal throughout. Furthermore, serum from the

tenth passage was injected into two volunteers who remained well but who later developed Colorado tick fever on being challenged with serum from a natural instance of the disease.

The infectious agent of Colorado tick fever is an extremely small virus, comparable in size to that of yellow fever and poliomyelitis, two of the smallest human infecting agents.

The virus of Colorado tick fever shows many interesting properties.⁴ It is remarkably stable, surviving for at least three and a half years either in the ice compartment of an ordinary refrigerator or in a commercial deep freeze unit. It can be preserved by freezing and drying although the virus seems to be initially weakened by this procedure. The disease can be transmitted to the hamster in the usual dosage in dilutions of 1:1000. Healthy hamsters caged with sick animals do not acquire Colorado tick fever even after eating those that died of the disease.

The evidence for the tick transmission of Colorado tick fever is entirely circumstantial. The two original human volunteers fed adult male and female ticks for the duration of the disease. The progeny were carried through a complete cycle. Some of the nymphs and adults were fed separately on susceptible human subjects, but failed to transmit Colorado tick fever.⁵ The experimental work going on at the present time on this phase of the problem has not progressed to the point where definite conclusions can be drawn.

It remains to develop a laboratory test that will confirm the clinical diagnosis. However, a diagnosis can be made with a high degree of accuracy based on the clinical history, course, and hematological study of each case. In Colorado the history of exposure to ticks, the dengue-like symptoms and fever curve are characteristic of no other disease, since dengue does not occur in this part of the United States.

SUMMARY

Colorado tick fever is a virus disease, presumably tick-borne. It has been presented as a regional disease. Like Rocky Mountain spotted fever it may be found to occur much more extensively than is now supposed. It is a distinct disease entity related neither to Rocky Mountain spotted fever nor to dengue which it clinically and hematologically closely resembles.

BIBLIOGRAPHY

1. BECKER, F. E.: Tick-borne infections in Colorado, *Colorado Med.*, 1930, xxvii, 36, 87.
2. TOPPING, N. H., CULLYFORD, J. S., and DAVIS, G. E.: Colorado tick fever, *Pub. Health Rep.*, U.S.P.H.S., 1940, lv, 2224.
3. FLORIO, L., STEWART, M. O., and MUGRAGE, E. R.: The experimental transmission of Colorado tick fever, *Jr. Exper. Med.*, 1944, lxxx, 165.
4. Unpublished data.
5. Personal communications.

6. SHAFFER, F. C.: Personal experiences with Colorado tick fever, *Colorado Med.*, 1935, xxxii, 226.
7. FLORIO, L., HAMMON, W. McD., LAURENT, A., and STEWART, M. O.: Colorado tick fever and dengue. An experimental immunological and clinical comparison, *Jr. Exper. Med.*, 1946, lxxxiii, 295.
8. STEWART, M. O., FLORIO, L., and MUGRAGE, E. R.: Hematological findings in the golden hamster, *Jr. Exper. Med.*, 1944, lxxx, 189.
9. BLACK, W. C., FLORIO, L., and STEWART, M. O.: A histologic study of the reaction in the hamster spleen produced by Colorado tick fever virus, *Am. Jr. Path.* In press.
10. FLORIO, L., STEWART, M. O., and MUGRAGE, E. R.: The etiology of Colorado tick fever, *Jr. Exper. Med.*, 1946, lxxxiii, 1.

ASSOCIATION OF ACUTE PULMONARY LESIONS WITH INFECTIONS OF THE THROAT *

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Fort Bragg, North Carolina

IN a three year study of respiratory illness among soldiers, three groups of diseases have caused the great majority of hospital admissions, namely, exudative tonsillitis and pharyngitis, primary atypical pneumonia, and undifferentiated respiratory disease. Other specific diseases such as influenza and the contagious exanthemata constituted a small and easily recognized group. Investigation of the cases of exudative tonsillitis and pharyngitis disclosed that approximately 25 per cent of them had clinical features, bacteriological findings, and an antibody response indicative of streptococcal infection; another 25 per cent harbored β -hemolytic streptococci but did not have the clinical features or the antibody response characteristic of streptococcal infections. Half of the patients with exudative tonsillitis and pharyngitis had neither clinical, bacteriological, nor serological evidence of streptococcal infection and the cause of the illness remained unknown.¹ The second commonly encountered disease, primary atypical pneumonia, was recognized by its characteristic roentgenographic lesion and distinctive history, physical findings, and clinical course.² Undifferentiated acute respiratory disease was a diagnosis made by exclusion in patients who did not have roentgenographic evidence of a pulmonary lesion, and did not have streptococcal infection, or exudative tonsillitis and pharyngitis.

In the progress of these studies a number of patients have been encountered in whom pulmonary lesions demonstrable by roentgenograms have been associated with exudative tonsillitis or pharyngitis due to the streptococcus or of unknown cause. Instances have also been found of the association of pulmonary lesions with streptococcal infections not producing exudate in the throat.

These cases have been of interest from several points of view. They raised the question of whether or not two distinct etiologic entities were con-

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currently infecting the patients. Conversely, they might be explained as instances of pneumonia due to β -hemolytic streptococcus or other agents producing pulmonary lesions similar to those usually called primary atypical pneumonia. In the absence of specific tests or criteria for the diagnosis of primary atypical pneumonia, the problem cannot be settled at the present time. Nevertheless the cases themselves are thought to be of sufficient interest to warrant presentation of some illustrative examples.

PULMONARY INFILTRATION ASSOCIATED WITH EXUDATIVE PHARYNGITIS
DUE TO β -HEMOLYTIC STREPTOCOCCUS

The following three cases are representative of the group exhibiting clinical and laboratory evidence of streptococcal pharyngitis or tonsillitis associated with pulmonary infiltration of the type usually seen in primary atypical pneumonia.

Case 1. A 19-year-old soldier was admitted to the hospital on April 13, 1943, one week after induction in the Army, complaining of sore throat, cough, chest pain, feverishness, and headache. Four days before admission, he noted the onset of sore throat of moderate severity, followed by nasal obstruction and discharge, hard cough accompanied by the production of sputum, substernal discomfort, and hoarseness. Two days later, headache, feverishness, chilliness, malaise, and anorexia developed.

On initial examination on the fifth day of illness, the patient was only mildly ill. The pharyngeal and tonsillar mucosa were slightly injected and there were a few discrete spots of tonsillar exudate. The cervical lymph nodes were moderately en-

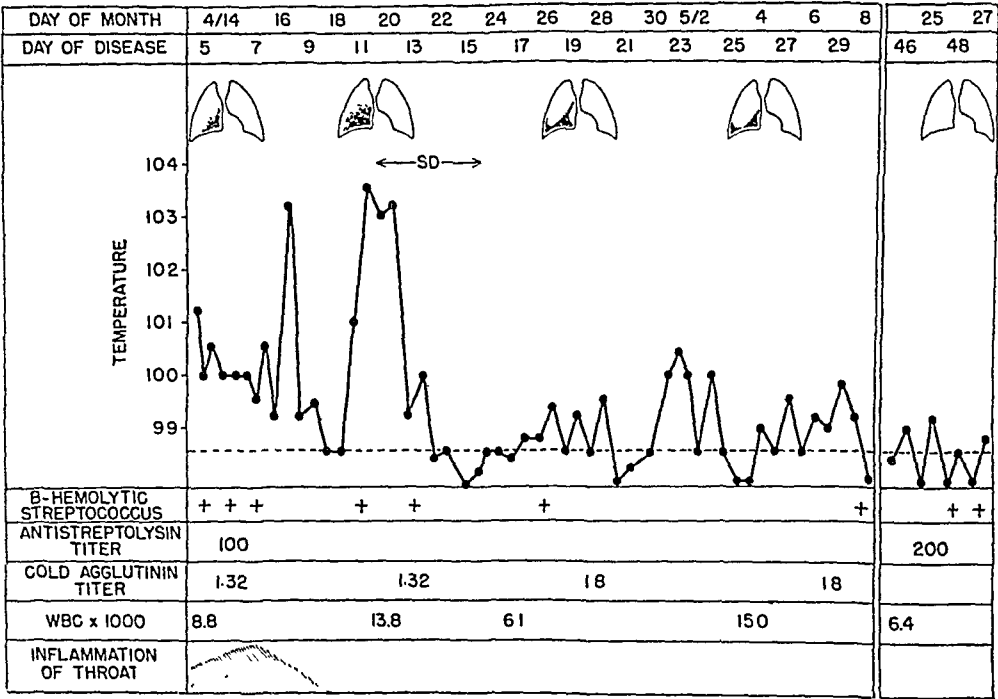


FIG. 1. (Case 1). Exudative tonsillitis due to β -hemolytic streptococcus and pulmonary infiltration resembling primary atypical pneumonia.

larged. β -hemolytic streptococci of group A, type 9, were recovered in throat cultures. The course of the illness and pertinent laboratory data are depicted in figure 1.

In the two days following hospital admission, the pharyngeal mucosa and particularly the soft palate became intensely red and edematous, presenting the appearance typical of peritonsillar cellulitis; without specific treatment this reaction subsided in a few days, as did the swelling of the lymph nodes.

A roentgenogram of the chest taken on the fifth day of illness revealed irregular hazy areas of increased density at the base of the right lung. Physical signs of pneumonia were not detected until the eighth day of illness. On the eleventh day of disease, the temperature rose to 104° F. at which time roentgenographic and physical findings indicated involvement of most of the right lower lobe. A blood culture taken at the height of the febrile reaction remained sterile. Sulfadiazine was administered in usual dosage for three days without apparent effect on the course of the pulmonary disease, although the temperature approached normal. The patient's subsequent course was consistent with atypical pneumonia, and was characterized by prolonged low-grade fever, slow clearing of the pulmonary lesion, and the production of copious amounts of mucopurulent sputum. A roentgenogram of the chest on the forty-eighth day of illness revealed completely clear lung fields.

Comment. This patient apparently had a simultaneous onset of pharyngitis and atypical pneumonia. Throat and sputum cultures contained β -hemolytic streptococci throughout the entire hospital course, and a rise in antistreptolysin titer in the serum was found. Whether the pulmonary lesion was caused by β -hemolytic streptococcus or whether the latter was a secondary invader complicating primary atypical pneumonia cannot be stated with certainty. The course of the pulmonary disease was certainly not of the type generally thought to be characteristic of hemolytic streptococcal pneumonia. The presence of cold agglutinins may be considered a point in favor of the view that the pulmonary lesion was due to primary atypical pneumonia.

Case 2. This 20-year-old soldier, with three months of military service, was admitted to the hospital on April 20, 1943 complaining of sore throat. The day before admission he developed a sore throat followed shortly by feverishness, chilliness, headache, malaise, and anorexia. At the time of initial examination he appeared mildly ill with signs of a mild streptococcal tonsillitis. β -hemolytic streptococci of group A, type 5, were recovered from throat cultures. The tonsils and soft palate were moderately swollen, the mucosa diffusely injected, and there were large confluent patches of exudate on the tonsils and uvula. The cervical lymph nodes were somewhat enlarged. The temperature record and pertinent laboratory data are recorded in figure 2.

Without specific treatment, the symptoms and signs of tonsillitis subsided in the course of four to five days. At about this time, however, the patient began to complain of nasal obstruction and discharge, cough, substernal pain, and hoarseness, and began to raise moderate amounts of mucopurulent sputum. He continued to run a low-grade fever which rose occasionally to 101° F. Roentgenograms of the paranasal sinuses and of the lungs revealed normal findings. On the fifteenth day of illness, however, a very small lesion in the costophrenic angle of the right lung was revealed by roentgenogram, and on the twenty-second day this shadow was seen more clearly. At this time, fine inspiratory râles were detected for the first time over the right lower lobe. Râles were heard daily thereafter until the patient left the hospital on sick furlough on the twenty-eighth day of illness. No chemotherapy was administered during the illness.

Comment. This patient had acute exudative tonsillitis from which β -hemolytic streptococci were recovered. He subsequently developed a rise in antistreptolysin titer. Although the pharyngeal lesion subsided promptly, low-grade fever continued and, in the third week of illness, physical and roentgenographic evidence of a pulmonary lesion was demonstrated. Although β -hemolytic streptococci were isolated from the sputum at this time, the development and course of the pulmonary lesion was in keeping with a diagnosis of primary atypical pneumonia. It is interesting, however, that in this patient, cold hemagglutinins did not develop.

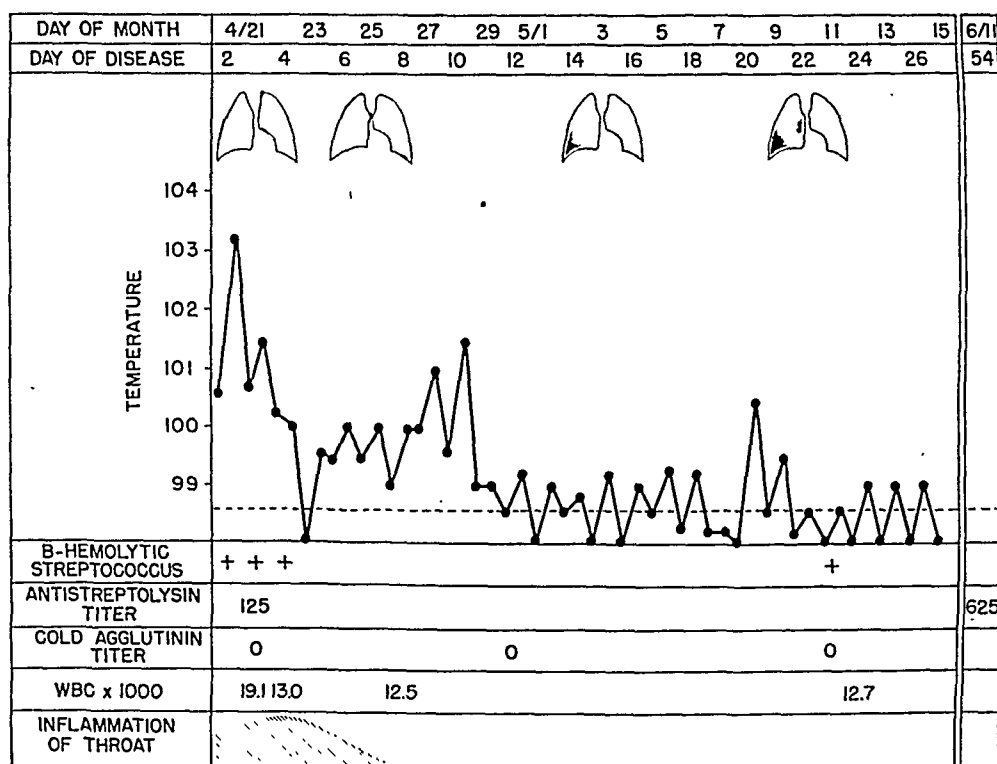


FIG. 2. (Case 2). Exudative tonsillitis due to β -hemolytic streptococcus and pulmonary infiltration resembling primary atypical pneumonia.

Case 3. This 20-year-old soldier, after one month in the Army, entered the hospital on May 12, 1943 complaining of chilliness, malaise, sore throat, and cough. He had mild symptoms of a cold for 10 days. On May 10 he developed sore throat, hoarseness, chilliness, feverishness, malaise, and headache.

On admission he appeared moderately ill. There was diffuse redness and edema of the soft palate. The pharynx and tonsils showed only injected vessels and a few pin point areas of exudate. The clinical impression was non-streptococcal exudative tonsillitis. The course of the illness and relevant laboratory data are shown in figure 3. The initial roentgenogram revealed no abnormalities in the lungs and the throat cultures on the first two hospital days did not contain β -hemolytic streptococci.

The patient appeared to be improving until the fifth day of illness, when it was noted that the tonsils and pharynx had become acutely inflamed and the cervical lymph nodes were enlarged and tender. Throat cultures now contained group A β -hemolytic

streptococci, type 3. The following day a diffuse scarlatinal rash appeared. The patient became quite ill and was given sulfadiazine from the eleventh to the sixteenth day of illness. During this time the appearance of the pharynx became normal and the skin rash faded.

On the eighteenth day of illness the patient developed substernal chest pain and fever, and physical examination revealed fine râles at the base of the right lung. A roentgenogram showed an area of increased density in this area. Sulfadiazine was again administered and the febrile reaction subsided. Fine râles were elicited by physical examination until the twenty-third day of illness. At the time of discharge, on the thirty-eighth day of disease, a roentgenogram of the chest showed a small area of increased density still present at the base of the right lung.

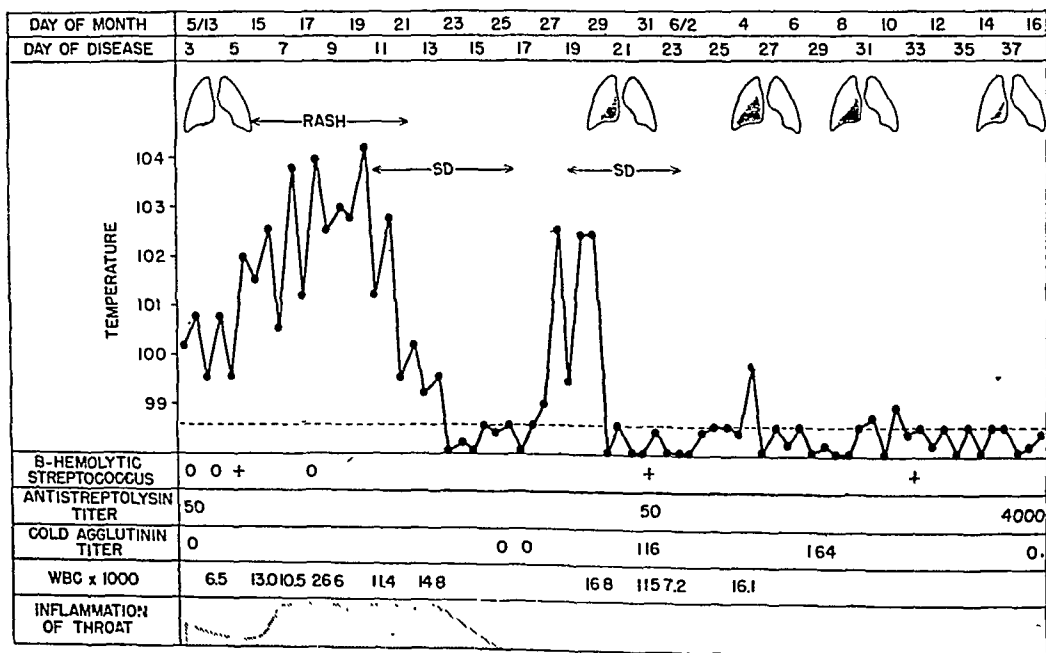


FIG. 3. (Case 3). Scarlet fever and pneumonia.

Comment. At the time of admission to the hospital this patient apparently had a non-streptococcal sore throat but subsequently developed scarlet fever and streptococcal pharyngitis. This was presumed to be an instance of hospital cross-infection. During convalescence from the streptococcal infection the physical and roentgenographic signs of pneumonia developed. Both streptococcal antibodies and cold hemagglutinins were later demonstrated in the patient's serum.

PULMONARY INFILTRATION ASSOCIATED WITH LABORATORY EVIDENCE OF STREPTOCOCCAL INFECTION

The following two cases are presented as additional instances of infection with β -hemolytic streptococci associated with pulmonary disease. In one instance (Case 4) the pulmonary lesion was demonstrated before the patient acquired his streptococcal infection.

Case 4 (figure 4). First admission. A 35-year-old white soldier with three months of military experience was admitted for the first time on March 19, 1944, with the complaint of cough and feverishness.

Illness began on March 17, with dry cough followed by feverishness, headache, anorexia, weakness, sore throat and hoarseness. On admission he appeared only mildly ill. The pharynx revealed no abnormalities and the chest was clear except for rhonchi. The temperature on admission was 100.2° F., rose to 102.6° F. that night and fell to normal on the fourth day. He was discharged on the sixth hospital day with a diagnosis of "common cold." Cough was still present on discharge but the other symptoms had abated. The day after admission fine râles were heard over the lower lobe of the right lung; these persisted for two more days but were not heard on discharge.

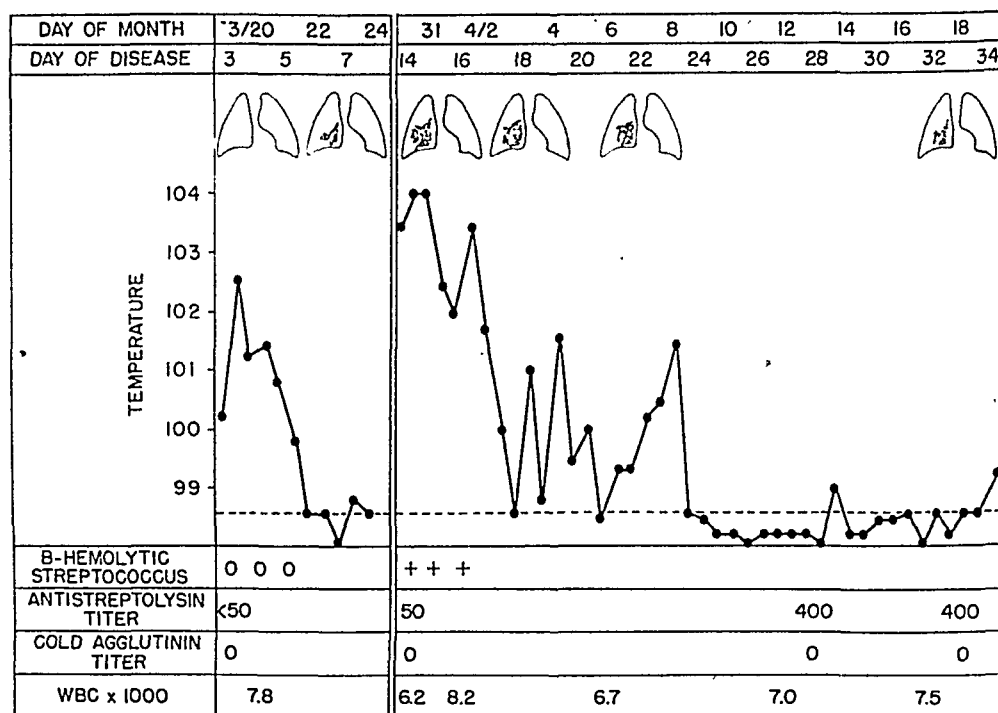


FIG. 4. (Case 4). First admission: primary atypical pneumonia. Second admission: primary atypical pneumonia and streptococcal pharyngitis.

The admission chest roentgenogram was normal but films on March 22 showed early peribronchial infiltration at the right cardiohepatic angle.

Throat cultures on March 19, 20, and 21 revealed no pathogenic organisms. On the day before discharge the bed next to him was occupied by a patient with hemolytic streptococcal pharyngitis. Unfortunately subsequent throat cultures were not made on the patient.

Second admission. The patient was readmitted on March 30, 1944, six days after leaving the hospital. In the interim he continued to cough and felt weak. He noted irritation and soreness of the throat. On March 26 he again became feverish and chilly and these symptoms persisted until he was readmitted.

Physical examination revealed no abnormal findings in the throat. There were fine and coarse râles over the lower lobe of the right lung and chest roentgenograms confirmed the presence of pulmonary infiltration. The temperature on admission was 103.4° F. and it remained elevated above 100° F. for a week. The patient was weak

and worn out, coughed and raised mucopurulent sputum but was not dyspneic or cyanotic. The pulse rate was not more than 100 even though the temperature was 104° F. The throat appeared benign. The course of the pneumonia, although protracted, was uneventful and recovery was eventually complete. No chemotherapy was administered during either hospital admission.

Total and differential leukocyte counts remained within normal limits during both hospital admissions.

Throat cultures on March 30, 31, and April 1, all contained moderate numbers of β -hemolytic streptococci of group A (not typable).

Sputum on April 1 contained a heavy growth (+++) of β -hemolytic streptococci of group A (not typable) and no other pathogenic bacteria.

During convalescence a diagnostic rise in antistreptolysin titer was demonstrated but cold hemagglutinins did not develop.

Comment. This case rather clearly demonstrates the concurrent existence of two separate diseases. In the first admission bacteriological study indicated freedom from streptococcal infection and at the same time the early stages of atypical pneumonia were present. Just before discharge he was exposed to a case of streptococcal infection in an adjacent bed and presumably was infected from that source. Premature return to duty may have caused an exacerbation of the pulmonary infection and on the second admission, a week later, he exhibited the characteristic course of a moderately severe case of atypical pneumonia. There was no clinical evidence of streptococcal infection. The antibody response could have been that of a streptococcal carrier.³ Although the presence of streptococci in the throat and sputum suggested the diagnosis of streptococcal pneumonia, the clinical course was not characteristic of that infection. Moreover, if streptococcal pneumonia was present it must have been superimposed on primary atypical pneumonia since the latter clearly was present before the patient acquired his streptococci.

Case 5 (figure 5). An 18-year-old white soldier with less than one month's military service, was admitted to the hospital on March 23, 1944, complaining of chilliness and cough.

For about a week he had nasal obstruction and discharge and a non-productive cough. The day preceding admission he became feverish and had an exacerbation of the cough which was now associated with substernal discomfort and with the production of sputum. Later he became chilly, developed headache, felt weak, and noted sore throat.

On admission he appeared only mildly ill. The lungs were clear to physical examination. The uvula and pharynx were moderately injected and the former was edematous. The tonsils were large and swollen. However, there was no exudate and the appearance of the throat was not characteristic of streptococcal pharyngitis. The cervical lymph nodes were not enlarged or tender.

The redness and edema of the throat subsided the next day and he improved symptomatically. The maximum temperature of 103° F. was reached on the day after admission, but fever above 100° F. persisted for five days. On the third hospital day chest roentgenogram showed pulmonary infiltration in the left lower lobe, and at the same time râles were heard at the left lung base and these persisted for about one week. Convalescence was uneventful and the soldier was returned to duty on June 9.

Total and differential leukocyte counts were within the normal range during the illness.

Throat cultures on the first three hospital days showed β -hemolytic streptococci; the first and third contained group C organisms, the second group A, type 12. Sputum culture on March 30 revealed no significant pathogenic bacteria.

A diagnostic rise in antistreptolysin titer was demonstrated during convalescence but cold hemagglutinins did not develop.

Comment. In this case there appeared to be concurrent infection with atypical pneumonia and hemolytic streptococci of both groups A and C. The streptococcal infection was extremely mild, almost inapparent. It seemed unlikely that a streptococcal infection of this character would produce a bacterial pneumonia.

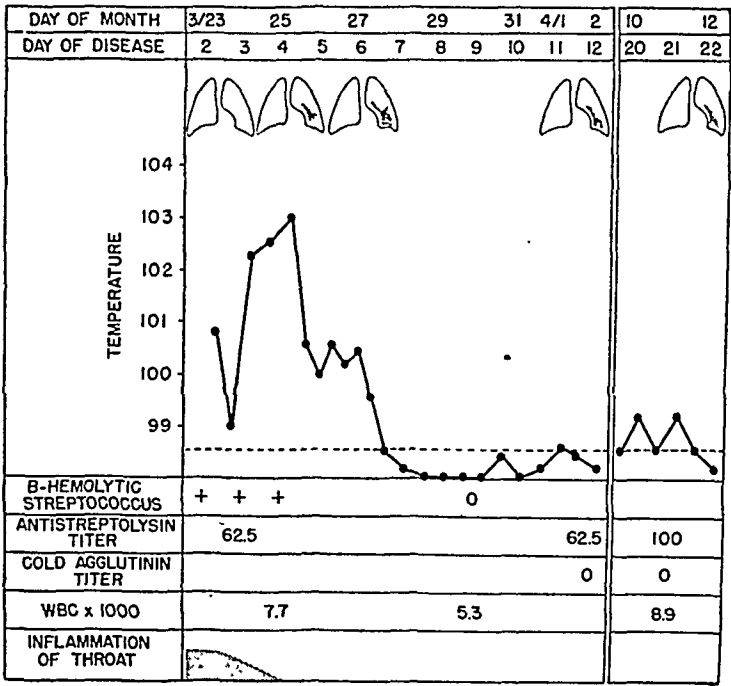


FIG. 5. (Case 5). Streptococcal pharyngitis and pulmonary infiltration resembling primary atypical pneumonia.

PULMONARY INFILTRATION ASSOCIATED WITH NON-STREPTOCOCCAL EXUDATIVE PHARYNGITIS AND TONSILLITIS

The final two cases presented are examples of non-streptococcal exudative pharyngitis and tonsillitis associated with pulmonary infiltration. In both of these cases the pharyngeal exudate persisted almost as long as the pulmonary lesion and may well have been etiologically related to it.

Case 6 (figure 6). A 23-year-old white soldier with two months of military service was admitted to the hospital on March 18, 1944, complaining of chilliness and fever.

Until the onset of the present symptoms he had been in good health. On the day before admission, he noted nasal stuffiness, and later in the day became chilly and then feverish.

On admission he did not appear seriously ill. The pharynx was moderately injected and the uvula and soft palate reddened and somewhat edematous. The lungs were clear and the physical examination otherwise negative. The temperature was 103.8° F.

The next day the pharyngeal and tonsillar mucous membranes were still only moderately injected but there was a large patch of confluent white exudate on the pharyngeal wall and several tiny spots of exudate on the tonsils. The tonsillar exudate increased in size so that by the sixth day of illness each tonsil was covered with a thick green, dirty-looking necrotic membrane having the appearance of Vincent's infection. On the same day, crackling râles were detected for the first time in the region of the left lung posteriorly and a roentgenogram revealed infiltration throughout the entire left midlung field.

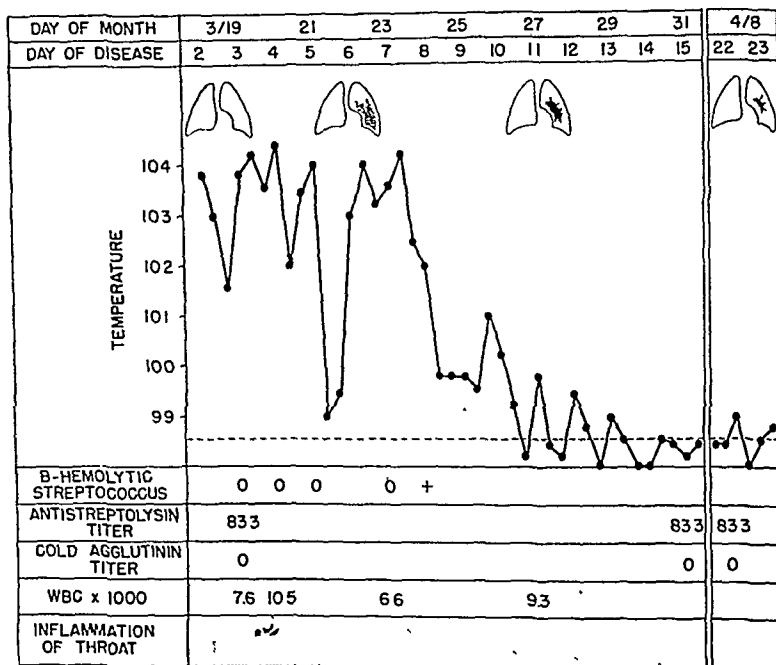


FIG. 6. (Case 6). Vincent's tonsillitis and pneumonia.

The patient maintained an elevation of temperature above 104° F. for four days, and above 100° for nine days. Despite the high fever, at no time did he appear seriously ill, and there was no dyspnea or cyanosis. The pulse was not elevated in proportion to temperature; while the latter was 104°, the pulse was 100.

Cough began on the sixth day of illness and was productive of only moderate amounts of mucopurulent sputum, which was never bloody, and was at no time foul-smelling. Likewise there was no fetor oris despite the presence of extensive exudate on the tonsils. The cervical lymph nodes were not enlarged or tender.

The patient slowly improved. The tonsillar exudate decreased in size until only small patches remained on the ninth day of illness, but the latter persisted for another week. The chest became clear to physical examination on the twenty-second day of illness.

Sulfadiazine was begun on the third hospital day but was discontinued within 24 hours because of albuminuria. Thereafter, aside from general supportive measures, only hydrogen peroxide and sodium perborate mouth washes were used.

Total and differential leukocyte counts were within normal limits throughout the illness.

Throat cultures on March 19, 20, 21 and 24 showed no significant pathogenic bacteria. A type 9 pneumococcus was present on several occasions, and a few colonies of group F β -hemolytic streptococci on one occasion. Fusiform bacilli and spirochetes in moderate numbers were found in smears of the tonsillar exudate. Cultures of the sputum revealed only normal flora.

No rise in antistreptolysin titer was found in convalescent phase sera. Cold hemagglutinins likewise were absent.

Comment. The development, progression, and resorption of the tonsillar exudate seemed to parallel the development and recession of the pulmonary lesion. This might suggest a single etiology for both lesions. On the contrary, the throat infection resembled Vincent's angina in appearance whereas the pulmonary lesion was not indicative of a lung infection caused by anaerobic organisms.

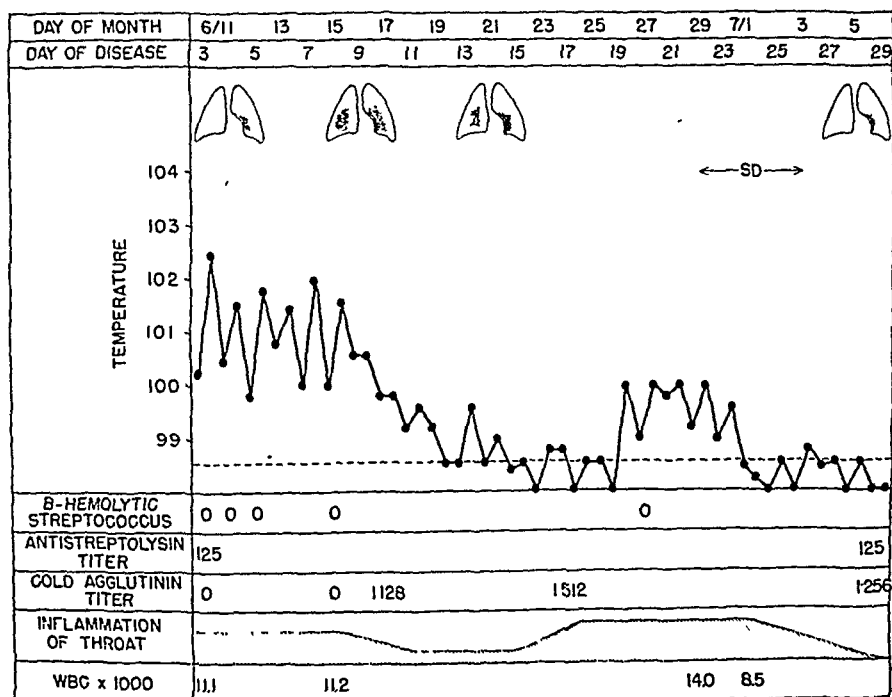


FIG. 7. (Case 7). Exudative tonsillitis and pharyngitis of unknown etiology and pulmonary infiltration resembling primary atypical pneumonia.

Case 7 (figure 7). A 19-year-old white soldier with three months of military service was hospitalized on June 10, 1943, complaining of cough, sore throat, headache, and fever.

Illness began on June 8 with sore throat and dry cough. The next day the patient developed a headache and shortly before admission became feverish and chilly, and complained of aching in the muscles of the back. The cough became productive and was accompanied by substernal distress.

The patient appeared moderately ill, and exhibited nasal obstruction and discharge and redness of the pharynx with prominent swollen red lymphoid follicles on the

posterior pharyngeal wall. The tonsils were small and moderately but diffusely injected, and had a small amount of streaky white exudate on their surface. The uvula was quite diffusely red and slightly edematous. The appearance of the throat was not typical of streptococcal pharyngitis. The cervical lymph nodes were not enlarged or tender. The lungs were clear and the rest of the physical examination yielded only normal findings. A small patch of pneumonic infiltration in the left lower lobe, along the cardiac margin, was seen in the chest roentgenogram obtained on admission.

The illness ran a protracted febrile course and throughout the patient appeared apathetic and listless, coughed and raised mucopurulent sputum and complained of anorexia and headache. The temperature varied between 100° and 102° F. during the first week, was below 99.2° for the next nine days, then rose again to 100° for four days, and finally returned to normal limits. Râles in the chest were first detected on the tenth day of illness. Clinically and by roentgenogram there was a spread of the pneumonia to involve both right and left lungs. The signs of inflammation in the throat, particularly the redness of the uvula and pharynx and the amount of exudate on the tonsils and on the posterior pharyngeal wall, seemed to wax and wane, being more intense during the two febrile peaks and subsiding in the afebrile interval. The patient was returned to duty on July 9, one month after admission, with the pharynx normal in appearance and the lungs clear. Sulfadiazine was given from June 29 to July 3.

The total leukocyte count was 11,100 per cu. mm. on admission but rose to 14,000 late in the course of the illness. Differential leukocyte counts were normal.

Throat cultures on June 10, 11, 12, 15, and 17 revealed only normal bacterial flora. Two blood cultures were sterile. Three sputum examinations for acid-fast bacilli were negative and smears of the sputum showed no fusiform bacilli or spirochetes.

No rise in titer of antistreptolysin was demonstrated but the cold hemagglutinin titer rose to 512.

Comment. In this instance the pharyngeal and tonsillar exudate and inflammation seemed to be an integral part of the disease since it waxed and waned with the febrile course and persisted as long as the pulmonary lesion.

DISCUSSION

It is axiomatic in clinical practice to attempt whenever possible to explain all manifestations of illness in a patient on the basis of a single etiologic diagnosis. In the face of clinical, bacteriological, and serological evidence of streptococcal infection of the throat it is reasonable to assume that an associated pulmonary lesion is probably also due to streptococcal infection, and indeed, there is no undisputed method to refute that diagnosis. In no instance, however, among the cases presented, did the clinical features of the pneumonia fit the usually accepted picture of streptococcal pneumonia.^{4, 5, 6} Although some of the cases had relatively high temperatures, they were of short duration and the patients did not appear profoundly ill. The pulse was relatively slow as compared with the temperature response. None of the patients exhibited more than minimal respiratory distress. None developed pleural effusions. During the course of the pneumonia the leukocyte count was normal or only moderately elevated. Sulfonamide therapy may perhaps have affected the febrile course but did not appear to shorten the duration of

the pulmonary disease and the course in untreated patients was similar to that in treated patients. If these cases did represent instances of streptococcal pneumonia, it is therefore necessary to revise current concepts of the clinical characteristics of that infection and to recognize that hemolytic streptococcus may cause a benign, transient, uncomplicated pulmonary infiltration similar in its clinical pattern to that produced by primary atypical pneumonia of unknown cause.

Streptococcal pneumonia appears to be a relatively uncommon complication of streptococcal pharyngitis. In a recent food-borne epidemic of septic sore throat involving 100 hospitalized patients, none developed pneumonia.³ A similar absence of pneumonia following epidemic streptococcal pharyngitis has been reported by others.⁷

All of the clinical features of the pulmonary lesion in these cases which were regarded as not characteristic of streptococcal pneumonia were those which are commonly found in primary atypical pneumonia. The onset was relatively slow, the general condition of the patients good, the pulse slow despite high temperature, the pulmonary infiltration developed and resolved slowly, and the signs of respiratory embarrassment were minimal. Moreover, the physical signs and roentgenographic picture were entirely consistent with those usually found in primary atypical pneumonia.² The development of cold hemagglutinins in some of the cases supported this diagnosis. The failure to obtain cold hemagglutinins in some of the cases may be related to the age of the sera at the time the tests were performed.⁸ Cold hemagglutinins were demonstrated in three of the four cases (1, 2, 3, and 7) in which the tests were performed within three months after the collection of the sera. In the three cases (4, 5, and 6) in which tests were delayed from 11 to 15 months after the specimens were obtained cold hemagglutinins were not found. In a previous study, however, it was found that even when freshly obtained sera were tested, less than half of the cases of atypical pneumonia developed cold hemagglutinins.⁹

The cases presented were selected from two study groups observed in two years during the spring of 1943 and 1944. In each group approximately 900 consecutive respiratory admissions from selected organizations were seen. All patients had roentgenograms of the chest; all were examined for the presence of exudate in the throat. Data were therefore at hand to determine the incidence of atypical pneumonia, streptococcal infections, and exudative tonsillitis and pharyngitis, both streptococcal and non-streptococcal. Atypical pneumonia accounted for 14 per cent of the admissions for respiratory disease during the first study and 7.5 per cent during the second study. In both years exudative pharyngitis and tonsillitis due to hemolytic streptococcus accounted for approximately 3.5 per cent of the admissions; exudative tonsillitis and pharyngitis of unknown cause were responsible for 6.5 per cent of admissions. With the data available, it was not possible to demonstrate any relationship, other than a fortuitous association, between the occurrence

of pulmonary infiltration and either streptococcal or non-streptococcal exudative tonsillitis. In this regard, two recent reports are of interest, describing what was believed to be a fortuitous association of malaria and primary atypical pneumonia.^{10, 11}

The relation between non-streptococcal exudative tonsillitis and pharyngitis and pulmonary infiltrations, although it appeared statistically fortuitous, was clinically more obscure. In the course of these studies the impression was gained that in some instances the pharyngeal infection and the pulmonary lesion represented concurrent but independent infections. This seemed particularly likely in those instances in which exudate was present at onset and disappeared within a few days while the pulmonary lesion continued to evolve and persist for several weeks. Such a relationship was encountered in a number of cases. However, in the two cases described above the exudate in the throat persisted almost as long as the pulmonary lesion and seemed therefore to be more intimately related to it. This was particularly true of case 7. In case 6, on the other hand, the clinical impression of the exudative lesion on the tonsils was Vincent's infection while the pulmonary lesion was entirely consistent with primary atypical pneumonia and inconsistent with the usual course of anaerobic infection of the lungs. Smith,¹² and Pierce and Field,¹³ however, have pointed out that while the usual form of pulmonary fusospirochetosis is lung abscess and bronchiectasis, this may be preceded by acute pneumonitis which may resolve without reaching the stage of destruction of lung tissue. It is not possible, in the present case, to state whether the pulmonary and tonsillar lesions were independent or whether both were manifestations of fusospirochetal infection. This case of Vincent's angina was included in this report only as an illustrative example. In fact, however, Vincent's infections comprise a very small number of the group of cases termed exudative tonsillitis and pharyngitis of unknown etiology.¹

One other possible association of respiratory diseases has been suspected, namely, the occurrence of both primary atypical pneumonia and acute undifferentiated respiratory disease in the same individual. Unfortunately there are no laboratory tests by which the latter diagnosis may be made and even its clinical recognition is dependent solely on exclusion of other entities. By the definition used of undifferentiated respiratory disease, this condition and atypical pneumonia are mutually exclusive. Nevertheless numerous instances have been encountered in which the patient was admitted to the hospital with what appeared to be acute undifferentiated respiratory disease only to develop signs of atypical pneumonia a week or 10 days later. Recent studies on human volunteers suggest that acute undifferentiated respiratory disease may be immunologically distinct from atypical pneumonia.¹⁴ Epidemiological studies during certain years have demonstrated a parallel incidence of the two diseases during the winter months.¹⁵ Until specific diagnoses can be made for both conditions the relationship between the two must remain speculative.

SUMMARY

Representative cases of the association of acute pulmonary infiltration and infections of the throat have been presented. Some of the upper respiratory infections were due to β -hemolytic streptococcus and others had exudate of non-streptococcal origin. The pulmonary lesions were of the type usually seen in primary atypical pneumonia. The relationship between the throat and pulmonary lesions was discussed. It was suggested that in some instances they may have been related while in others the association was probably fortuitous.

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BIBLIOGRAPHY

1. Commission on Acute Respiratory Diseases: Endemic exudative pharyngitis and tonsillitis, *Jr. Am. Med. Assoc.*, 1944, cxxv, 1163-1169.
2. DINGLE, J. H., ABERNETHY, T. J., BADGER, G. F., BUDDINGH, G. J., FELLER, A. E., LANGMUIR, A. D., RUEGSEGG, J. M., and WOOD, W. B.: Primary atypical pneumonia, etiology unknown, *Am. Jr. Hyg.*, 1944, xxxix, 67-128, 197-268, 269-336.
3. Commission on Acute Respiratory Diseases: A study of a food-borne epidemic of tonsillitis and pharyngitis due to β -hemolytic streptococcus, type 5, *Bull. Johns Hopkins Hosp.*, 1945, lxxvii, 143-210.
4. MILLER, J. L., and LUSK, F. B.: Epidemic of streptococcal pneumonia and empyema at Camp Dodge, Iowa, *Jr. Am. Med. Assoc.*, 1918, lxxi, 702.
5. CECIL, R. L.: Pneumonia and empyema at Camp Upton, N. Y., *Med. Clin. N. Am.*, 1918, ii, 567.
6. AMOSS, H. L., and CRAVEN, E. B.: Serum treatment of hemolytic streptococcus pneumonia, *Jr. Clin. Invest.*, 1933, xii, 885.
7. BLOOMFIELD, A. L., and RANTZ, L. A.: An outbreak of streptococcic septic sore throat in an army camp, *Jr. Am. Med. Assoc.*, 1943, cxxi, 315-319.
8. FINLAND, M., and BARNES, M. W.: Cold agglutinins. V. Deterioration of cold iso-hemagglutinins on storage, *Jr. Clin. Invest.*, 1945, xxiv, 490-496.

9. Commission on Acute Respiratory Diseases: Cold hemagglutinins in primary atypical pneumonia and other respiratory infections, *Am. Jr. Med. Sci.*, 1944, ccviii, 742-750.
10. FLEMING, J., LINDECK, E. W., and EVANS, I. H.: Primary atypical pneumonia. An epidemic associated with malaria, *Brit. Med. Jr.*, 1945, i, 689-693.
11. CAMPBELL, E. T.: Primary atypical pneumonia and malaria, *War Med.*, 1943, iii, 249-255.
12. SMITH, D. T.: Relation of Vincent's angina to fusospirochetal disease of the lungs, *Jr. Am. Med. Assoc.*, 1930, xciv, 23-26.
13. PIERCE, C. B., and FIELD, H.: Fusospirochetal pneumonia, *Am. Jr. Roentgenol.*, 1935, xxxiii, 451-467.
14. Commission on Acute Respiratory Diseases: Unpublished observations.
15. Commission on Acute Respiratory Diseases: Epidemiology of atypical pneumonia and acute respiratory disease at Fort Bragg, North Carolina, *Am. Jr. Pub. Health*, 1944, xxxiv, 335-346.

CARBON TETRACHLORIDE POISONING; A REPORT OF ONE CASE WITH NECROPSY AND ONE NONFATAL CASE WITH CLINICAL LABORATORY STUDIES *

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Two recent cases in which the patients were admitted to the United States Naval Hospital, Oakland, California, and in one of which the termination was fatal, attest to the medical importance of carbon tetrachloride intoxication. As will be mentioned later in the reports of cases, both men, by ignoring simple precautions in the matter of ventilation, exposed themselves to toxic quantities of the volatilized chemical. That physicians generally are not sufficiently aware of the dangers of exposure to carbon tetrachloride is evidenced by the failure to establish a correct diagnosis prior to entry in this hospital in either case, despite an easily obtainable history and rather characteristic findings.

That carbon tetrachloride (tetrachlormethane, CCl_4) is toxic and occasionally fatal to both man and experimental animals has been realized at least since 1909.¹ Its lethal action on man is effected chiefly by means of damage to the kidney, as has been appreciated since the report of Smetana.² In addition to developing this thesis, Smetana discovered and reported 141 cases, with 39 fatalities, in reviewing the literature up to 1938. Subsequently, Quadland³ cited approximately 300 cases, reported during the period 1932 to 1943, in nine of which the outcome was fatal. These resulted from occupational, but not necessarily industrial, use. He excluded from his series the nonindustrial fatality reported by Allison.⁴ In addition, in the literature of 1943 and 1944 we have found reports of six fatalities, summarized in table 1; three fatalities reported in 1945 are also included in the table.^{10, 11} Despite this impressive tabulation of the injurious action of carbon tetrachloride, its excellent solvent properties, coupled with its non-inflammability and inexpensiveness, have maintained its widespread use in industry and in the home. That fatal or even serious poisoning does not occur in well-regulated industries is evidenced by the report of Smyth and Smyth¹² and the more recent account of Stewart and Witts.¹³ A discussion in 1944 of industrial poisoning from carbon tetrachloride was concerned only with transient occurrences of nausea and vomiting presumably due to

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concentrations of less than the present legal standard maximum of 100 parts per 1,000,000¹⁴ in inspired air. Similarly, it will be seen in table 1 that most of the recent cases of fatal poisoning have occurred in isolated or individual use of carbon tetrachloride as contrasted to its use in industry.

The clinical picture of headache, nausea and vomiting, with occasional hematemesis, followed by mild icterus and later by oliguria, anuria and retention of nitrogen, is repeatedly described in the reports of cases appearing

TABLE I
Deaths Due to Carbon Tetrachloride and Reported in the Recent Literature

Reported by	Cases	Deaths	Circumstances in cases in which death occurred
Allison, B. R. ⁴	2	1	The patient was an alcoholic who drank an unknown quantity of carbon tetrachloride by mistake.
Sanford, S. P. ⁵	1	1	A seaman used a bottle of carbon tetrachloride to clean his hands, forearms and shoes, and died three hours later. Necropsy showed pulmonary edema.
Konwaler, B. E., and Noyes, C. B., Jr. ⁶	3	1	Poisoning followed exposure in a closed compartment in which 1½ quarts of carbon tetrachloride had been volatilized. Two other persons simultaneously exposed recovered. (Necropsy)
Sherman, S. R., and Binder, C. F. ⁷	4	1	The patient was cleaning a bomb sight in a room with poor ventilation and was overcome by fumes two or three times during the exposure. (Necropsy)
Forbes, J. R. ⁸	3	1	French seamen; exposure in a small, poorly ventilated compartment while cleaning clothes in fire extinguisher fluid.
Willcutts, M. D. ⁹	3	2	
Dillenberg, S. M., and Thompson, C. M. ¹⁰	20	1	All cases occurred on a submarine, following volatilization of carbon tetrachloride. Fatality due to pulmonary edema nine days after exposure. (Necropsy)
Eddy, J. H., Jr. ¹¹	Unspecified	2	Ten patients, all ill enough to be hospitalized. Exposure occurred in process of manufacture of a land mine. "A tremendous amount of the chemical was vaporized in a closed room having no mechanical ventilation."

in the literature and is likewise exemplified by the reports which appear later in this paper. Pulmonary complications, such as edema and pneumonia, may occur as late as a week or more after exposure, as is emphasized by the reports of Smetana² and of Dillenberg and Thompson.¹⁰ Although experimental proof is lacking, the inference is justified that some of the carbon tetrachloride is removed from the body by means of the expired air as well as by the kidney. This is said to be true of dogs, in which renal excretion is

TABLE II
Laboratory Data in Case 2*

Date, July	Blood chemical data								Weight, pounds	Urine				Other tests	
	C.C.	I.L.	CO ₂	B.U.N.	N.P.N.	Cl.	P. Prot.			Chol.	Quantity c.c.	U.N.	Alb.		Cells
							Total	Albumin							
5	3	25.4								125/80	None			Kahn negative Hgb. 12.5 gm. WBC 11,600 Segs. 69%; Lymphus. 31%	
6		30.8		62.5				4.7	3.3	140	525 Specific gravity 1.010	2	Loaded with RBC	Chest x-ray negative Platelets 202,860	
8		21.7		70.3	91.5			5.1		155	2,105	5.1	Neg.	EKG normal Serum calcium 10.7 U.U. 1.80 Clotting time 3½ min.	
11	1	11.6	64			396				190/120	2,580 Specific gravity 1.015		Neg.	WBC 8,050, Segs. 72% Erythrocyte sedimenta- tion rate 11 mm.	
14				30.8		462		6.15	4.5		2,800	6.5	Neg.	Creatinine 2.1 Hgb. 14.5 gm. RBC 4,420,000	
19		15.2		22.8	51.7					140/90	3,000		Neg.	Urea clearance 48% Visual fields and fundi normal	
23	Neg.	11.7		17.2	40.9			8.1	4.2		3,100		Neg.	Platelets 320,000	
25										125/80	2,900		Neg.	Urea clearance 82% Sulfobromophthalein retention 45 min. 20% 60 min. 5%	

* Alb.—Qualitative urine test for protein.

Sugar was not present in any specimen examined.

B.U.N.—Blood urea nitrogen, expressed as milli-

grams per 100 c.c. of blood.

C.C.—24 hour cephalin-cholesterol flocculation test;

graded 1-4

Chol.—Blood cholesterol.

Cl.—Blood chloride expressed as NaCl.

Normal range 450-500.

Clotting time—Test tube method.

CO₂—Carbon dioxide combining power, c.c. per 100

c.c. of plasma.

EKG.—Electrocardiogram.

Hgb.—Hemoglobin (Haden-Hauser).

I.I.—Icteric index.

Lymphs.—Lymphocytes.

N.P.N.—Nonprotein nitrogen expressed as milligrams

per 100 c.c. of serum.

Platelets—Method of Fonio.

P. Prot.—Plasma proteins.

RBC—Red blood cells.

Segs.—Segmented cells.

Serum calcium—Expressed as milligrams per cent.

Sedimentation rate—Cutler method.

U.N.—Urine urea nitrogen in grams per 24 hours.

U.U.—Urine urobilinogen in dilution (ratio).

WBC—White blood cells.

minimal and renal pathologic changes are correspondingly not conspicuous.¹⁵ Further, while anuria or oliguria is the primary physiologic disturbance in man, the development of pulmonary edema is often the immediate cause of death.

Return of the damaged organs to their normal state has been presumed to follow clinical recovery. That this is actually true would seem established by the thorough investigation by Corcoran, Taylor and Page¹⁶ of one case of recovery from the poisoning, and by the case of Simon,¹⁷ in which necropsy 10 months after recovery from the poisoning did not reveal any residual signs of the intoxication, death being due to an unrelated cardiac disease.

Our second case, in which the diagnosis was established soon after admission of the patient, was rather thoroughly studied by means of hepatic and renal functional studies, blood chemical examinations and observation of blood pressure and weight. These findings are summarized in table 2. The early rise of blood pressure to a level of 190 mm. of mercury systolic and 120 mm. diastolic, with a subsequent fall to normal, is of some interest. The fall of blood pressure occurred coincidentally with a loss of weight, which in turn reflected the clinical disappearance of edema.

CASE REPORTS

Case 1. An enlisted man, 24 years of age, became ill on the evening of February 6, 1945. At this time he was nauseated and vomited. The following morning he was free of symptoms but later on the same day he had a sudden chill, which was followed by fever and increasing nausea. By the morning of February 8 he complained of pain in the vicinity of both kidneys and was passing grossly bloody urine. He was admitted to the hospital the next day. On admission his temperature was 100° F., pulse 100, respirations 22, blood pressure 138 mm. of mercury systolic and 80 mm. diastolic. His face was flushed and he was vomiting bile-stained liquid. The abdomen was diffusely tender and there was bilateral tenderness of the costovertebral angles. There was no edema of the extremities nor clinical evidence of jaundice.

At this time a history of daily exposure over a period of six months to carbon tetrachloride in a large, open vat was obtained. The patient also admitted the rather liberal use of alcohol. On the day before the onset of his symptoms, which happened to be rainy, he had shut himself in his car while he cleaned his uniform and the upholstery of the car with carbon tetrachloride.

Laboratory studies after admission showed that leukocytes numbered 15,800 per cu. mm. of blood with 86 per cent segmented and 7 per cent band forms. Erythrocytes numbered 4,300,000 per cu. mm. of blood. The urine was loaded with erythrocytes and contained albumin in maximal quantities. The concentration of nonprotein nitrogen was 90 mg. per 100 c.c. of serum, that of chlorides was 396 mg. per 100 c.c. of plasma and the carbon dioxide combining power was 67 vol. per cent per 100 c.c. of plasma. The prothrombin time was 73 per cent of normal; the cephalin-cholesterol flocculation was reported to be weakly positive. On the second day in the hospital the patient was visibly jaundiced and the icteric index was recorded as 58 units.

The patient was placed in an oxygen tent on admission and fluids containing 300 gm. of glucose and 1,000 c.c. of amigen were administered intravenously each day. Physiologic saline solution was given as needed to maintain blood chlorides within the normal range. Vitamins C, K and B complex (betalin) were included in the foregoing solutions. In spite of this treatment, the patient pursued an unfavorable course,

vomiting persisted and severe oliguria developed. He appeared drowsy, although mentally he was reasonably clear. The icterus gradually diminished, but the prothrombin time dropped to 50 per cent of normal, indicating progressively increasing hepatic damage. Erythrocytes disappeared from the urine but the daily output of urine fell below 100 c.c. The nonprotein nitrogen level rose to 174 mg. per 100 c.c. of serum. On the sixth hospital day the patient's face became edematous and the fluid intake was accordingly reduced to 1,500 c.c. daily. During the night of February 15, he complained of failing vision and retinoscopy showed a minimal degree of papilledema. Two hours later he became delirious and a series of clonic convulsive seizures developed. His temperature was recorded as 101.4° F. A spinal tap showed clear fluid under increased pressure. On the following morning he coughed up a small amount of blood-tinged frothy sputum and thereafter there was clinical and roentgenologic evidence of bilateral pneumonia. He died the following afternoon.

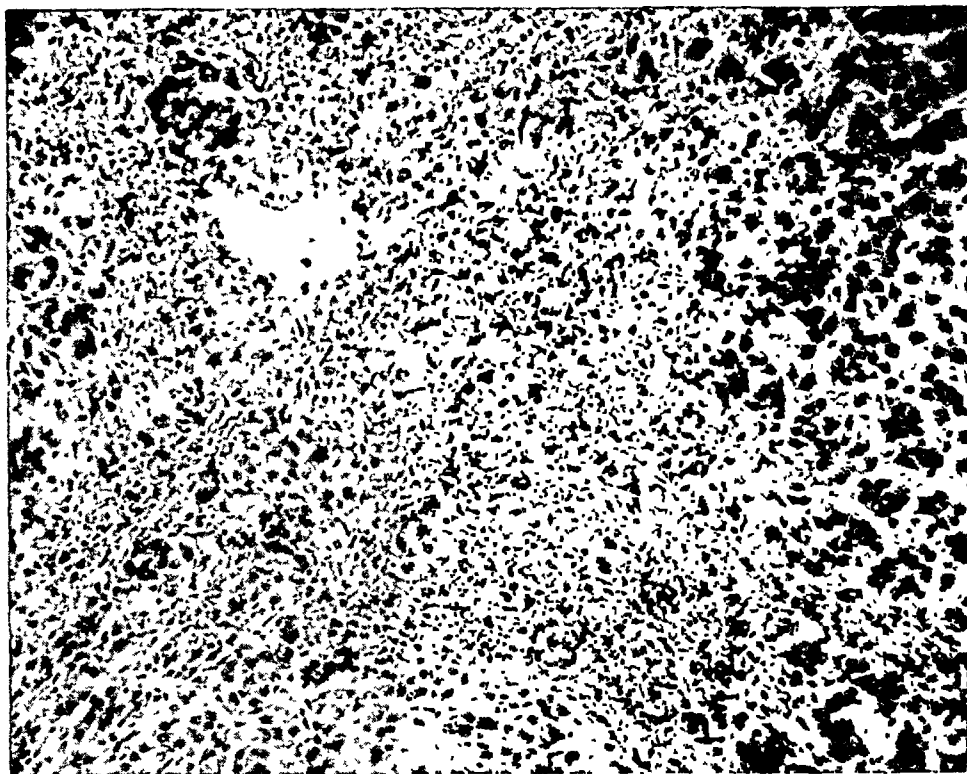


FIG. 1. Focal necrosis of liver, mostly in lobular centers, with advanced autolysis and loss of cell structure. Fairly heavy infiltration of inflammatory cells, largely neutrophils.

Necropsy. The body was that of a well-developed white man. There was slight pitting edema of both ankles and the face was also edematous. Both conjunctivae were moderately edematous and definitely icteric. Bilateral pleural effusions were present with approximately 100 c.c. of clear fluid on the left and 150 c.c. of slightly yellowish, cloudy fluid on the right. Both lungs were definitely heavier than normal, the right weighing 1,115 gm. and the left 1,096 gm. On section, the parenchyma bulged slightly above the cut surface and an excess of free fluid escaped from the cut surfaces of all lobes. Small patches of pneumonic consolidation were present within the right upper lobe and diffusely scattered throughout both lobes of the left lung. The liver weighed 1,784 gm. and presented a mottled appearance. It was yellowish red. Both kidneys were enlarged, the left weighing 218 gm. and the right 294 gm.

The capsules stripped easily from both cortices, revealing smooth, yellowish surfaces. On section, the surfaces were greasy and yellowish gray, the differentiation between cortex and medullary portions being relatively indistinct.

Microscopically the most marked changes were observed in the liver and the kidneys. Scattered throughout the liver (figure 1) were foci of necrosis, mostly located about the lobular centers but in some places extending through the midzonal region to the periphery of the lobules. The hepatic cells in the centers of the affected portions showed advanced autolytic changes with complete loss of structure of many of the cells. The loss of supporting hepatic cells in affected regions allowed marked dilatation of the hepatic sinusoids, all of which were packed with erythrocytes. Many large macrophages were scattered throughout the necrotic regions and these contained ingested pigment granules. There was early proliferation of fibrocytes throughout the lobules of the liver but no apparent regeneration of hepatic cells was noted in any

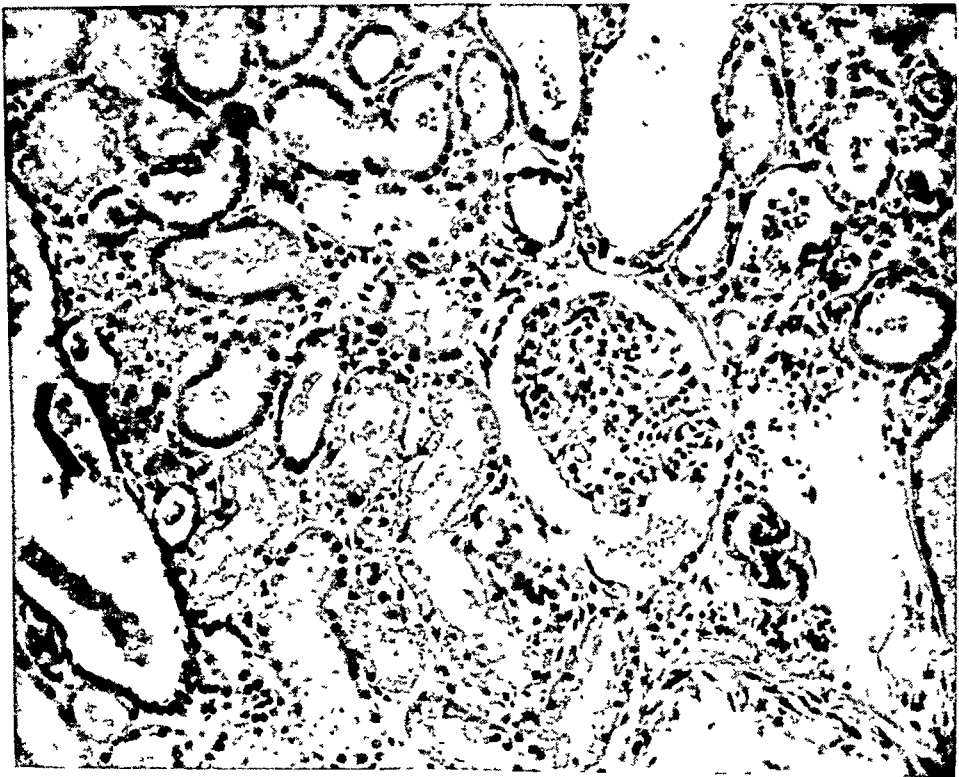


FIG. 2. Note destruction of renal tubule cells, with loss of nuclei and desquamation of cells.

sections studied. There was no evidence of proliferation in the bile ducts in the affected regions. Inflammatory cells, particularly neutrophils, were infiltrated throughout the affected regions. Many focal collections of lymphocytes were also present about some of the smaller bile ducts. Fat stains showed lipoid droplets within the cytoplasm of many of the hepatic cells, especially at the periphery of the regions of focal necrosis.

Microscopically there were no glomerular changes in the kidneys (figure 2) except for some deposition of debris within the glomerular capsules. However, in both convoluted tubules and the loops of Henle there was marked destruction of the tubular epithelium. The cells were granular and many were completely degenerated. Numerous droplets of lipoid material were also demonstrable in the majority of the tubular cells on special staining.

The spleen (figure 3) presented regions of early necrosis in the central portion of some of the germinal centers, characterized by cellular destruction and early proliferation of fibrocytes with an increase of inflammatory products in these regions.

Microscopically, the lesions in the liver appeared to be the older. Those in the kidney appeared to be more recent, corresponding to the clinical course in this particular case. The splenic lesions were interesting, being similar to those demonstrated in cases of acute epidemic hepatitis by Wood.¹⁸ In this case the splenic lesions were much less advanced than the lesions in Wood's cases, perhaps because the hepatic damage was not nearly as extensive.

Case 2. An enlisted man, 22 years of age, on the afternoon of June 30, 1945, spent an hour in an inadequately ventilated ship's compartment, measuring 20 by 12 by 10 feet, cleaning his uniform with a pint of carbon tetrachloride; he could not be sure how much was volatilized. Two other men who spent brief periods in the com-

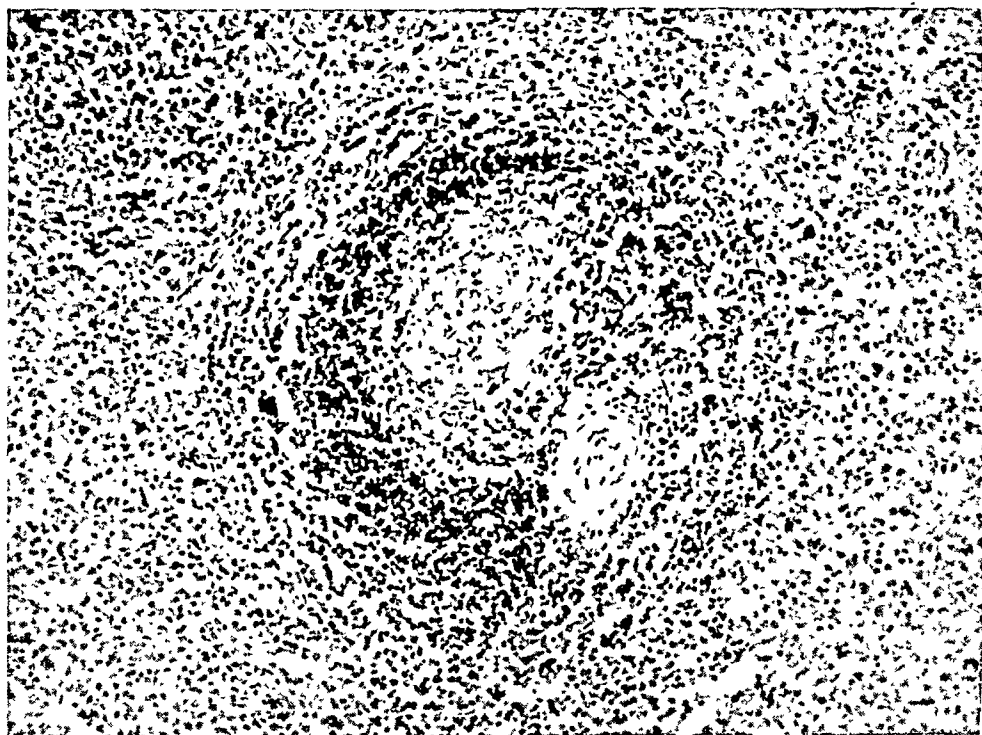


FIG. 3. Small regions of necrosis in germinal centers of spleen.

partment did not suffer ill effects. The patient was recovering from an infection of the upper part of the respiratory tract and it was at first difficult to distinguish the symptoms of that condition from the early effects of his exposure; subsequent developments, however, left no doubt that a toxic quantity of the chemical had been inhaled. The patient did not note any startling effects for 24 hours, during which time he ingested an allegedly small quantity of alcohol. The following day, 48 hours after the exposure to carbon tetrachloride, a headache, a temperature of 101° F. and protracted vomiting with hematemesis developed. He was transferred to the hospital on July 5.

On admission his temperature was 100° F.; the pulse was 90; the respiratory rate 25 per minute; the blood pressure 125 mm. of mercury systolic and 80 mm. diastolic. Physical examination showed a drowsy patient, who was vomiting re-

peatedly. There was a left subconjunctival hemorrhage. The liver was questionably palpable and the upper part of the abdomen diffusely tender. The patient was anuric during the first 24 hours; urinalysis on the following day revealed albumin and erythrocytes in quantity. By the second day facial edema was obvious and laboratory tests showed evidence of both hepatic damage and retention of nitrogen.

During the next week the edema markedly increased and then rapidly subsided. The blood pressure rose to a high point of 190 mm. of mercury systolic and 120 mm. diastolic, remained at this level for some days and returned to normal after three weeks. The urinary volume, which at first was very small, gradually increased to normal, although the urea content of the urine remained low. Concomitantly the patient lost weight and felt subjectively improved. The temperature was elevated in the evening to 100° F. until the tenth day in the hospital. Table 2 summarizes the laboratory data. It will be noted that electrocardiograms taken during the period of hypertension did not show any abnormalities and that roentgenographic examination of the thorax did not reveal any pathologic changes. It is of interest, in view of the report of Wirtschafter,¹⁹ that the visual fields were not altered. One month after the patient's exposure, when clinical recovery was apparently complete, the concentration of urea in the blood was normal, as was the urea clearance. However, the sulfo-bromophthalein liver functional test, with a dose of 5 mg. per kilogram of body weight, showed abnormal retention (20 per cent at 45 minutes and 5 per cent at 60 minutes).

Despite the anuria and edema, solution of dextrose, saline solution and amigen were administered intravenously and, since there was an increasing output of urine, administration was continued until the third day in the hospital, when the patient was able to retain liquids given orally. Vitamins C, B and K were administered as in the previous case. The protracted vomiting was relieved after the stomach had been thoroughly washed with solution of sodium bicarbonate. Thereafter, a full diet high in carbohydrate and protein was given with the addition of 1 gm. of choline hydrochloride three times a day. The occipital headache present from the onset outlasted all other symptoms as well as signs of renal insufficiency; 50 per cent solution of glucose given intravenously did not relieve it. Six weeks after admission the patient was transferred to another hospital for a month's convalescence prior to return to duty.

Based primarily on the work of Minot and Cutler,²⁰ who noted that low calcium levels increased susceptibility to carbon tetrachloride poisoning, calcium gluconate is frequently administered intravenously in treating acute carbon tetrachloride poisoning. In addition, the usual supportive measures, oxygen and intravenously administered fluids should be employed. When anuria occurs, the physician faces the dilemma of the need for fluids and the patient's inability to excrete them. Confronted with this, Hagen and his associates²¹ employed diathermy over the renal region and felt that this was instrumental in the favorable outcome in their case. Although portal cirrhosis due to carbon tetrachloride has been described,²² hepatic damage is usually a minor part of the problem with reference to human beings. The amino acid methionine and lipotropic substances, such as choline, are being given a clinical trial in mitigating the hepatic damage²³ and appear to have some promise.

COMMENT

Data are presented on two cases of carbon tetrachloride intoxication, in one of which the termination was fatal. The rôle of alcohol as an adjuvant

to the toxicity of this compound is suggested in both cases. In view of the widespread and almost indiscriminate use of this solvent the likelihood of encountering future cases is great. The diagnosis is made by observing combined hepatic and renal damage in a patient giving a history of recent or prolonged exposure to this compound. The clinical phenomenon most to be feared is progressive oliguria or anuria. Treatment consists in administration of specific nutriment for the damaged liver and the provision of adequate fluids to counteract the loss by vomiting and to improve renal elimination. Administration of oxygen is thought by some to be of benefit and should be used with penicillin in the not uncommon event of pneumonia. Obviously the best and most effective treatment is prophylaxis; this consists simply in never using carbon tetrachloride without adequate ventilation.

BIBLIOGRAPHY

1. HAMILTON, ALICE: Industrial toxicology, 1934, Harper & Brothers Publishers, New York, 329 pp.
2. SMETANA, HANS: Nephrosis due to carbon tetrachloride, *Arch. Int. Med.*, 1939, lxxiii, 760-777.
3. QUADLAND, H. P.: Carbon tetrachloride: Part 2 of a literature study of reports of occupational injuries attributed to volatile solvents, *Indust. Med.*, 1943, xii, 821-828.
4. ALLISON, B. R.: The treatment of acute carbon tetrachloride poisoning; with a report of two cases, *Ann. Int. Med.*, 1942, xvi, 81-93.
5. SANFORD, S. P.: Carbon tetrachloride poisoning, *U. S. Nav. Med. Bull.*, 1943, xli, 1486-1488.
6. KONWALER, B. E., and NOYES, C. B., JR.: Carbon tetrachloride poisoning; report of cases, *California and West. Med.*, 1944, lxi, 16-20.
7. SHERMAN, S. R., and BINDER, C. F.: Hazards of carbon tetrachloride in present-day use, *U. S. Nav. Med. Bull.*, 1944, xliii, 590-599.
8. FORBES, J. R.: Carbon tetrachloride nephrosis, *Lancet*, 1944, ii, 590-592.
9. WILLCUTTS, M. D.: Quoted by Konwaler, B. E. and Noyes, C. B.⁶
10. DILLENBERG, S. M., and THOMPSON, C. M.: Carbon tetrachloride poisoning; a report of twenty cases with one death, *Mil. Surg.*, 1945, xcvi, 39-44.
11. EDDY, J. H., JR.: Carbon tetrachloride poisoning; a preliminary report on the use of methionine in hepatitis, *Jr. Am. Med. Assoc.*, 1945, cxxviii, 994-996.
12. SMYTH, H. F., and SMYTH, H. F., JR.: Safe practices in the industrial use of carbon tetrachloride, *Jr. Am. Med. Assoc.*, 1936, cvii, 1683-1687.
13. STEWART, A., and WITTS, L. J.: Quoted in: Carbon tetrachloride poisoning, *Lancet*, 1944, i, 570-571.
14. BOWDITCH, M.: Pros and cons of standardization in setting threshold limits, *Indust. Med.*, 1944, xiii, 728.
15. ROBBINS, R. H.: The absorption, distribution and excretion of carbon tetrachloride in dogs under various conditions, *Jr. Pharmacol. and Exper. Therap.*, 1929, xxxvii, 203-216.
16. CORCORAN, A. C., TAYLOR, R. D., and PAGE, I. H.: Acute toxic nephrosis; a clinical and laboratory study based on a case of carbon tetrachloride poisoning, *Jr. Am. Med. Assoc.*, 1943, cxxiii, 81-85.
17. SIMON, M. A.: Acute toxic nephritis due to inhalation of carbon tetrachloride fumes, *Canad. Med. Assoc. Jr.*, 1939, xli, 580-583.
18. WOOD, DAVID: Personal communication to the authors.

19. WIRTSCHAFTER, Z. T.: Quoted by Eddy, J. H., Jr.¹¹
20. MINOT, A. S., and CUTLER, J. T.: Guanidine retention and calcium reserve as antagonistic factors in carbon tetrachloride and chloroform poisoning, *Jr. Clin. Invest.*, 1928, vi, 369-400.
21. HAGEN, W. S., ALEXANDER, H. A., and PEPPARD, T. A.: Toxic effects of carbon tetrachloride; report of case, *Minnesota Med.*, 1940, xxiii, 715-718.
22. MADDING, G. F., and BUTT, H. R.: Hepatitis resulting from inhalation of carbon tetrachloride, *Proc. Staff Meet., Mayo Clin.*, 1938, xiii, 391-394.
23. BEATTIE, J., HERBERT, P. H., WECHTEL, C., and STEELE, C. W.: Studies on hepatic dysfunction. I. Carbon tetrachloride poisoning treated with casein digest and methionine, *Brit. Med. Jr.*, 1944, i, 209-211.

REITER'S DISEASE WITH PROLONGED AURICULO-VENTRICULAR CONDUCTION *

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IN a recent study of two cases that revealed a combination of features suggesting the diagnosis of Reiter's disease, transient auriculoventricular conduction defects were observed in the electrocardiographic tracings. These appear to be the first instances in which morbid effects upon the myocardium have been demonstrated during the course of this disease. Although the nature and pathogenesis of the cardiac involvement are yet to be clarified, recognition of such myocardial manifestations should dispel confusion in differentiating this obscure syndrome from other diseases.

Since the publication of the first report of Reiter's disease in 1916,¹ communications relating to this syndrome have appeared at irregular intervals. Only 45 cases were reported up to the moment of Lever and Crawford's contribution.² In many of these, however, the diagnosis had to be accepted hesitatingly since the diagnostic triad failed to evolve completely; in others, inconclusive bacteriologic search failed to eliminate a gonococcic or other infectious cause. A recent addition of three more cases was made by Colby.³ Although the reports have been sparse and predominantly of continental origin, it is quite likely that the disease is not as rare as the literature may indicate.

Reiter's disease is a self-limited illness of undetermined etiology that is characterized by the appearance of a triad of major manifestations consisting of urethritis, conjunctivitis, and arthritis. With one exception,² all of the reported cases have occurred in young male adults. Acute urethritis or conjunctivitis is usually the first manifestation and within a period of four to eight weeks evolution of the triad is complete. The arthritis, however, may initiate the clinical onset. The purulent urethral discharge is attended by burning, increased frequency of micturition, meatal itching, and terminal hematuria. The conjunctivitis is, likewise, purulent but sticky. Superficial punctate keratitis is a frequent concomitant finding. Varying arthralgias of a migratory character may precede the polyarthritis. The weight-bearing joints are usually subject to inflammatory invasion although the syndrome may emerge with conspicuously disabling monarticular involvement. The common joints to be affected are the knees, ankles, wrists, hips, and the elbows, but the metatarsophalangeal, sternoclavicular and temporomandibular joints and segments of the cervical spine are not immune. The symptoms and the clinical appearances of the diseased articulations are similar to those of infectious origin. The arthritis is of longer duration than the conjunctivitis or urethritis and reluctance of the offended joints to sub-

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side prolongs the period of active disease. Although permanent joint destruction has not been seen, clinical and roentgenologic changes of a rheumatoid character have been reported.² The chemical and cytologic alterations of the aspirated synovial fluid resemble those found in the specific infectious arthritides.⁴ The accompanying fever is moderate and chills are unusual. The course of the disease is self-terminated within one to five months, but recurrences of the entire triad or efflorescences of any of its elements may appear months or years after the initial onset. On the other hand, the conjunctivitis or urethritis may abate and recur one or more times during the course of activity. Complete recovery without sequelae or residual signs may be expected. Penicillin and the sulfonamides are considered therapeutically ineffective.

In a disease that awaits a better exposition of the pathogenesis, it is difficult to consider any manifestation as a complication. Indeed, extension of the disease processes to adjacent organs is exceedingly common and, occasionally, severe enough to dominate the entire clinical picture. In addition to the conjunctivitis and keratitis, other frequently recognizable ocular manifestations are episcleritis, iritis and iridocyclitis. The genitourinary involvement is not confined to the urethra, for catarrhal prostatitis, prostatic abscesses, vesiculitis, and hemorrhagic cystitis may be observed. Hydronephrosis, pyelonephritis, and ureteral obstruction may alter the common pattern of Reiter's disease to demand prompt consideration of surgical relief. Ulcerations about the meatal orifice, on the glans and behind the corona appear shallow and circinate with an exudative, crusting or dry surface. The oral lesions are characterized by erythema of the buccal mucous membranes, vesicle formation and, finally, denudation. Pharyngeal congestion, superficial glossitis, and a fine vesicular eruption of the lips may suddenly or insidiously become evident. The development of hyperkeratotic scales, particularly over the bony prominences, may make the skin eruption indistinguishable from gonorrheal keratosis blennorrhagica. Obviously such dermatitis, in the presence of urethritis, conjunctivitis, and arthritis makes differentiation of Reiter's disease from venereal keratosis blennorrhagica dependent solely upon careful and complete bacteriologic investigations. Hemorrhagic puncta or vesicles on the skin may antedate the keratotic lesions. Like the conjunctival and urethral inflammations, exacerbations and remissions of the dermal lesions may occur. Roentgenograms of the involved joints may show not only demineralization of varying degree, but also circumscribed areas of subchondral decalcification, periosteal proliferation, and narrowing of the joint spaces. Extreme difficulty may be encountered in separating these changes from those exhibited in rheumatoid arthritis.

The laboratory findings are not of diagnostic significance. The white blood cell counts fluctuate between 10,000 and 20,000 during the active state of the disease and the sedimentation rates are rapid. Pyuria, albuminuria and hematuria characterize the urinary findings on gross or microscopic

examination. Numerous pus cells can be found in the prostatic expressions. The bacteriologic, immunologic and microscopic studies of the exudates, tissues, lining membranes, and blood and cavity fluids do not contribute any pathognomonic findings.

Although the inflammatory phenomena lead one to assume that the disease is of an infectious nature, bacteriologic and immunologic studies have not uncovered the causative pathogenic agent. In Reiter's original investigation a spirochete was obtained from the blood of the subject; hence the designation of the disease by the title, "Spirochetosis Arthritica." Subsequent investigations, however, have invalidated the assumption that any spirillum could be related to the disease process. In spite of the striking similarity of Reiter's disease to systemic gonorrhea, smears and cultures of exudates from the genito-urinary tract, the conjunctival secretions and aspirated joint fluids have uniformly failed to reveal the presence of gonococci; blood cultures and urine cultures have not grown gonococcal colonies; and complement fixation tests performed at various stages of the disease have not disclosed any increased titers of specific antibodies. Agglutination reactions for *B. abortus* and brucellergin skin tests have presented negative results. Agglutination tests for dysentery strains have, in a similar manner, proved negative. Inclusion bodies have not been discovered in stained scrapings of the conjunctival, urethral or synovial membranes. Specific organisms could not be identified in smears from the oral and penile lesions. Cultures of macerated synovial tissue have been found sterile and inoculations of various animals have produced unsuccessful results. An extensive and detailed search by Bauer and Engelman⁴ for specific bacterial or virus bodies was entirely fruitless.

The etiology has been further obscured by impressions derived from clinical observations. Beiglböck^{5a} postulated that the disease was fundamentally an allergic manifestation with the genito-urinary, ocular and skeletal systems chiefly participating. The association of conjunctivitis, arthritis and balanitis with positive intradermal reactions to gonococcus vaccine in patients afflicted with gonorrheal urethritis has extended and supported this conception. Sherman, Bluementhal and Heidenreich⁶ concluded that a toxo-allergic mechanism could effect superimposed ophthalmic, dermal, and arthropathic responses in bacteriologically proved gonorrhea. Clinical experience prompted Epstein and Chambers⁷ to believe that oral, corneal and cutaneous lesions might be allergic manifestations when associated with gonorrheal urethritis. It must be emphasized, however, that the gonococcus could readily be identified in these cases, whereas in Reiter's disease such an etiology has never been established. To imply, then, that Reiter's disease is a transitional form of gonorrhea, the outcome of an infection wherein the causative agent has undergone morphologic alterations defying identification, is entirely speculative and untenable. Nor can one unreservedly accept Manson-Bahr's contention^{5b} that the entire syndrome is related to dysenteric polyarthritis with superimposed toxic features.

CASE REPORTS

Case 1. A 20-year old white male was entirely well until March 10, 1945 when aching of the left ankle appeared. For the following six days the affected joint showed surface heat, redness, and tenderness; motion and weight bearing became increasingly painful. On March 16, itching and smarting of both eyes were sensed and within 24 hours congestion, photophobia and a mucopurulent discharge developed. Simultaneously, a purulent urethral discharge appeared. The inflamed left ankle became increasingly worse and both knees became involved.

The family history was not contributory. Measles, scarlet fever, and chickenpox were the only previous illnesses. Sexual exposure was vehemently denied.

Although urethral smears on three successive days were negative for gonococci, 10 intramuscular injections of penicillin were administered at intervals of three hours, and penicillin solution was instilled into the conjunctival sacs every three hours for a period of four days. At the end of this time the eye symptoms abated and for the continuing urethral discharge and polyarthritis another course of 10 intramuscular penicillin injections was given. On March 27 the bilateral conjunctivitis recurred while the urethritis spontaneously vanished.

Hospital observation was undertaken March 28 for the mucopurulent conjunctivitis, bilateral superficial punctate keratitis, and the arthritis of the knees and left ankle. During the first four days, the temperature fluctuated between 96.8° and 100° F. and the pulse between 68 and 102. One drop of 4 per cent homatropine was instilled into each eye and metaphen ointment was applied continuously. At the end of the first week the conjunctivitis and keratitis cleared, the left ankle seemingly resolved but the knees remained swollen and painful. A distant apical systolic murmur was then detected for the first time. The urine sediment contained numerous clumps of pus cells; albuminuria (2 plus) was found; and the specific gravity measured 1.026. The white blood cell count was 11,100 of which 60 per cent were polynuclears, 34 per cent lymphocytes, and 4 per cent monocytes; the red blood cell count revealed 4,100,000 cells and the hemoglobin content was 82 per cent. The sedimentation rate on admission was 21 mm. (Wintrobe) and on April 16 was 30 mm. Electrocardiograms taken on April 1 and 15 exhibited PR intervals of .22 second and .24 second with rates of 92 and 88 respectively (figure 1). On April 26 the skin surrounding the urethral meatus became reddened; two days later a yellow-brown crust on an erythematous base about 1.5 cm. in diameter appeared immediately proximal to the glans. No pain, itching, or bleeding was experienced. The inflamed joints persisted throughout the entire course.

On May 11, 1945 hospital transfer was effected. The subject appeared chronically ill, emaciated, pale and unable to maintain the erect posture owing to pain and weakness of the lower extremities. The conjunctivae were normal in appearance; ophthalmoscopic examination was negative. Membranes of the hard and soft palates were sites of many pin-point vesicles surrounded by adjacent erythema; the tongue revealed several painless, denuded, sharply margined, coalescent areas on the dorsal and lateral surfaces; the pharynx was coated by a mucopurulent, post-nasal discharge. Mastication and deglutition could be accomplished asymptotically. The heart was regular, the rate was 120, and no abnormalities could be detected; the blood pressure was 116 mm. Hg systolic and 74 mm. diastolic. A diffuse, shotty lymph node enlargement could be demonstrated in the anterior and posterior cervical, the epitrochlear, axillary and inguinal regions; splenomegaly or hepatomegaly was not found. A circular erythematous base, partly covered by yellow crusts, extended about the urethral orifice for a distance of .5 cm. Immediately proximal to the corona on the right dorsal surface, a non-indurated, painless, superficial ulcer about 1.5 cm. in diameter with a clean base was visible. Both knee joints were enlarged and an increased amount of fluid in the left suprapatellar area could be palpated; the left ankle appeared

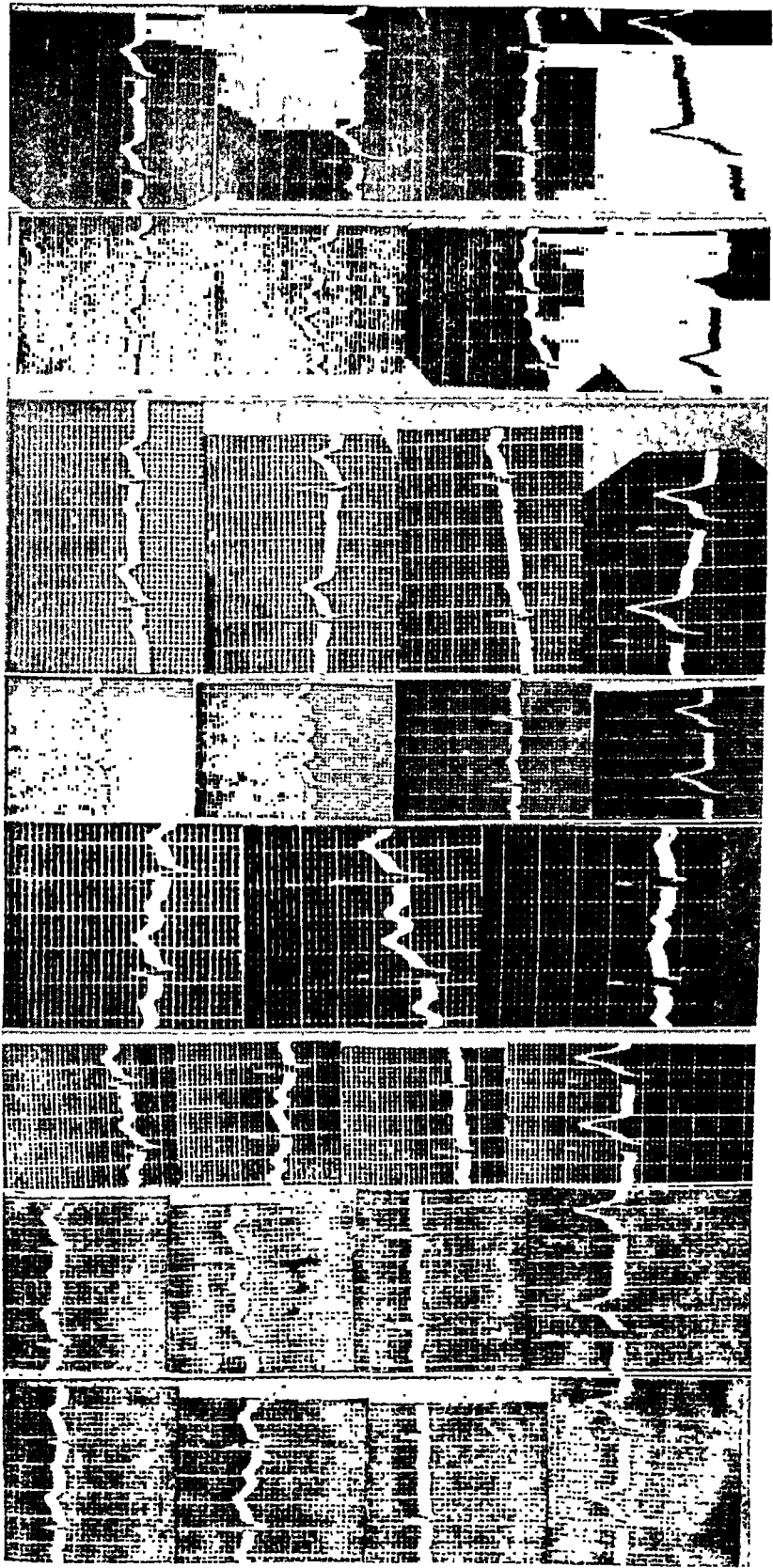


Fig. 1.

swollen. Painless motion could be executed in the involved joints, but both thighs and calves showed atrophy of the muscles attended by weakness and marked fatigability. An urethral discharge could not be expressed but the prostate was of a boggy consistency. The soles of both feet were covered with considerable keratotic deposits.

The arthritic condition improved slowly with radiant heat therapy and massage. Ambulation was undertaken with increasing ease and strength, although the swelling and stiffness of the joints persisted for four weeks. The thigh and calf muscles gradually increased in tone and size. The vesicular lesions of the oral membranes disappeared within a few days. In spite of the daily ingestion of 10 mg. of thiamine chloride, 150 mg. of nicotinamide and multiple vitamin capsules, the erythematous blush on the hard and soft palates persisted. During the third week an erythematous patch over the left buccal membrane erupted and a clean, painless, superficial ulcer 1 cm. in diameter appeared opposite the third upper right molar tooth. The denuded areas of the tongue remained unaltered in appearance. Yellow-brown scales adjacent to the meatus and over the ulcer proximal to the glans were desquamated but continued to reappear at irregular intervals; penicillin solutions applied to the penile lesions failed to effect any response. During the first week of June, non-tender vesicles of millet-seed size erupted on both lips but disappeared spontaneously within three days.

The laboratory findings were not informative. Urethral smears repeatedly failed to show any gram-negative, intracellular diplococci. The urine sediment contained 15 to 50 white blood cells under high-power fields; the specific gravity ranged between 1.016 and 1.028; the urea clearance was 102 per cent of average; cultures of the urine recovered hemolytic *Staphylococcus aureus*. The prostatic secretion contained many white blood cells but no organisms resembling the gonococcus. Cultures of the prostatic fluid yielded colonies of staphylococci and streptococci. Several smears of the meatal and shaft lesions showed no spirochetes, Ducrey bacilli, or Donovan bodies; a few gram positive diplococci were found. On several occasions, Kahn and Wassermann tests were performed but none was positive; the Frei, tuberculin and brucellergin skin tests were negative. No response was obtained to the intracutaneous test for Ducrey bacillus infection. All white blood cell counts during the six weeks of hospitalization varied between 4,750 and 8,000 with normal differential counts; the red blood cells and hemoglobin remained at normal levels. The serum protein content was 6.5 gm. per 100 c.c. and the albumin and globulin fractions were 4.6 and 1.8 gm. respectively. The Westergren sedimentation rate was 32 mm. on admission, rose to 45 mm. at the end of May, but steadily declined to 6 mm. by the last week of June. Throat cultures were persistently negative for Beta hemolytic streptococci. No parasites or ova could be recognized in the stool specimens on three separate occasions. Agglutinin titers for *S. dysentery* and *S. paradysentery* (W) could not be detected. The serum uric acid content was 4.9 mg. per 100 c.c.

The early roentgenographic examinations of the knees showed soft tissue swelling and a general haziness, but no erosions of the articular cortices; views of the left ankle indicated a mild bony atrophy. The cardiac silhouette failed to show any abnormalities. Intravenous pyelograms did not reveal any pathologic alterations.

During the last week of June the urinalysis disclosed normal elements chemically and microscopically. About 20 pounds of weight had been gained by mid-June and the fatigability and weakness were entirely overcome. The buccal lesions had entirely disappeared, the lingual areas of denudation had receded considerably, and lymph node enlargement was barely detectable. The consistency of the prostate was firmer. Subjectively and objectively the previously involved joints were normal; roentgenograms of the ankles and knees failed to disclose any periarticular swelling, haziness, articular changes, or bony atrophy. Clinically, cardiac abnormalities were at no time observed and serial teleroentgenograms remained normal.

Reëxamination on August 7 indicated that a gain of 30 pounds had been effected and that no clinical manifestations of the original disease were present except for a small superficial ulcer at the edge of the corona that measured .5 cm. in diameter. The urinary, hematologic, immunologic, cutaneous, cultural, prostatic, and stool tests were repeated with uniformly negative results. Scrapings from the small ulcer base, Kahn and Wassermann reactions were persistently negative and uninformative. The serial electrocardiograms showed the following changes in the P-R intervals (figure 1):

April 1, 194522 sec.
April 15, 194524
May 14, 194524
May 22, 194523
June 11, 194524
June 25, 194519
July 16, 194522
August 10, 194520

Case 2. A 23-year old white male was seen on November 12, 1944, for an urethral discharge and increased frequency of urination of two days' duration. He had been well until July 1944 when a paronychia of the right index finger required incision and drainage. In August 1944 an infection of the left external ear and a bursitis of the left shoulder had been successfully treated. On October 2, a cellulitis of the right calf necessitated incision and drainage.

The urethral and prostatic expressions contained numerous white blood cells but no organisms, and treatment was pursued in the form of daily prostatic massage. For the next two weeks a slight but constant terminal hematuria was observed. On December 2, 1944, photophobia, conjunctival congestion, and a mucopurulent discharge attended by bilateral iritis developed. He entered the hospital on December 4 with a temperature of 100.8° F. and a pulse rate of 98. Repeated smears of the urethral and prostatic fluids failed to show any organisms. Except for the urethral and conjunctival phenomena no other abnormal physical findings were encountered. On the second day of hospitalization the urethral discharge abruptly subsided after a seizure of lower abdominal pain that satisfactorily responded to the administration of enemata. Progressive swelling, limitation of motion, redness, heat and tenderness of the right wrist evolved during the first week while coincident vague pains of the left ankle were felt. Oral administration of sulfadiazine was begun immediately on December 6, one gram being given every four hours for 12 doses. This therapy was replaced by the instillation of penicillin solution into the conjunctival sacs every two hours. After 48 hours eight doses of intramuscular penicillin, 20,000 units at three-hour intervals were administered. A rhinitis appeared on December 11 that was quickly followed by congestion, vesiculation, and shallow ulcerations of the membranes of the tongue, gums, pharynx and cheeks. Anorexia, painful mastication, and painful deglutition were moderately severe. A second course of penicillin, 20,000 units every three hours, was initiated and maintained for one week during which time the oral manifestations disappeared. On December 18 frank inflammatory involvement of the left knee and ankle became evident and the signs enveloping the right wrist were intensified. A balanitis developed on January 1, 1945: the urethral orifice, the peri-urethral surface of the glans and the corona were covered with a brown crust resting upon a red base. Slow improvement of the eyes, joints, and genitalia followed but not until mid-February had all the phenomena vanished. On January 15 a bilateral axillary lymphadenitis prompted the administration of 20,000 units of penicillin every four hours for five days; the therapy was fortified by the application of hot compresses. The small amount of turbid fluid that drained through sinuses in the right axilla contained *Staphylococcus albus*. For the first 42 days the oral temperature fluctuated

between 99° and 101.8° F. Precordial pains were experienced at irregular intervals but never attended by objective clinical manifestations.

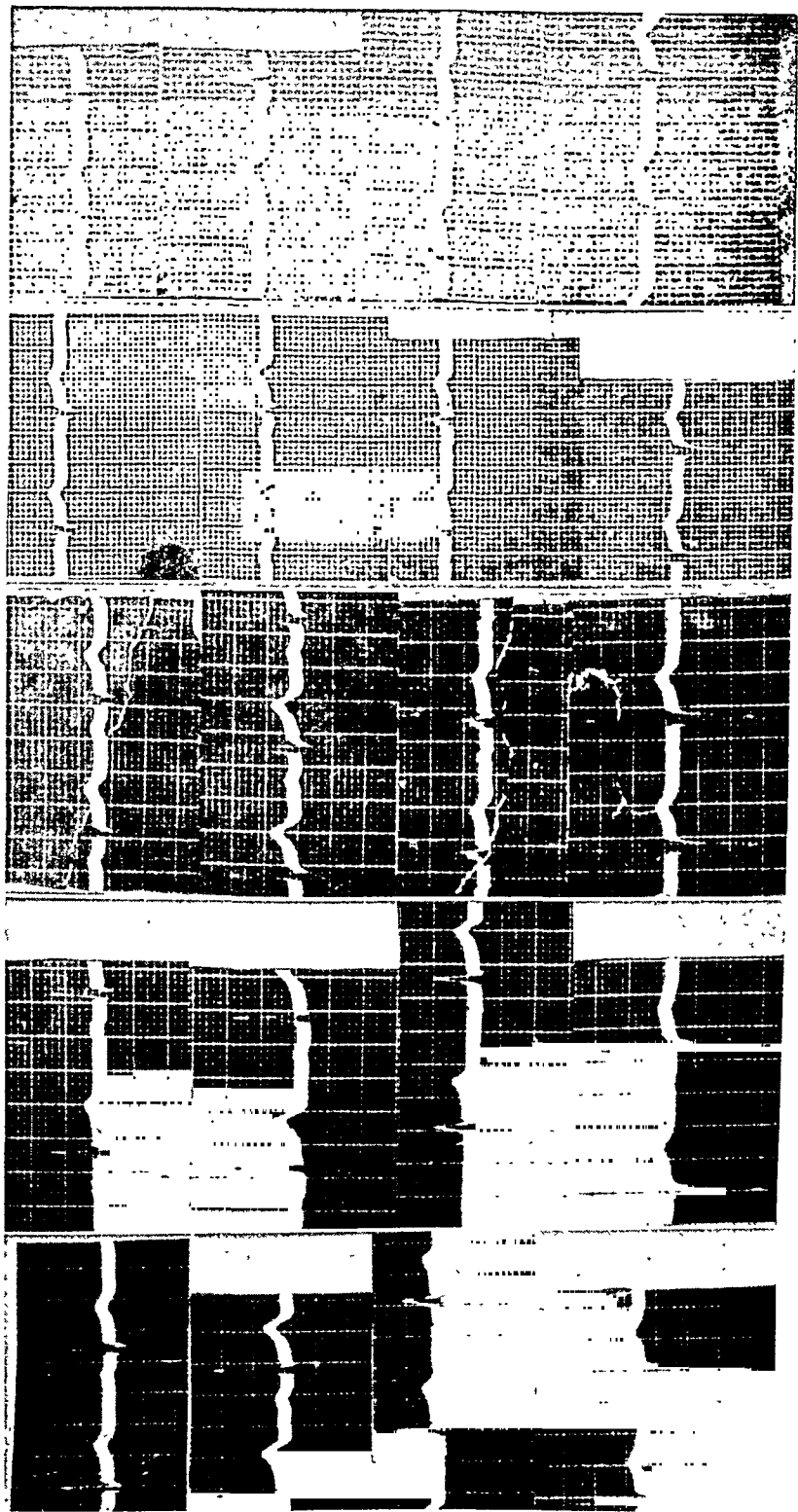
Diagnostic laboratory data could not be obtained. Smears and cultures of the eyes at the height of the infection revealed *Staphylococcus albus*. The urine was cloudy, the sediment loaded with white blood cells and clumps, and the test for albumin was 4 plus; 1 to 8 red blood cells were observed in the sediment under high-power fields on several occasions. These abnormal urinary elements disappeared on February 1. The white blood cell count on admission was 11,800 of which 84 per cent were polynuclear cells; the red cells and hemoglobin were normal; the non-protein nitrogen was 24, and the Westergren sedimentation rate was 40 mm. per hour. Until the latter part of January the leukocyte counts varied from 9,800 to 14,400 but thereafter normal values were obtained. Two blood cultures were made but remained sterile. Several Kahn and Wassermann tests proved to be negative. Roentgenographic visualization of the involved joints revealed a temporary mottled demineralization of the bones of the right wrist consistent with the conception of disuse atrophy. Pathologic states could not be identified in the cardiac silhouette, the lung fields, or flat abdominal plates.

In serial electrocardiographic tracings significant variations in the P-R intervals were measured. From January 23 to April 30, the duration of A-V conduction fluctuated between .18 second to .24 second (figure 2).

On May 17 the subject was transferred for further study. The cardiac findings were entirely negative except for an inconstant, localized, faint, systolic, apical murmur; the blood pressure was 134 mm. Hg systolic and 84 mm. diastolic. Palpable, shotty lymph nodes were found in both axillary and inguinal regions. The joints appeared normal, motion was unimpaired, and musculo-skeletal distress could not be elicited. The Westergren sedimentation rates failed to exceed 4 mm. per hour; the white blood cells varied between 6,400 and 7,100; the red blood cells and the hemoglobin determinations were normal. Blood cultures remained sterile; the serum uric acid content was 4.7 mg. per 100 c.c. Urine studies revealed no pathologic elements and only two or three white blood cells were counted under high-power fields; the urea clearance test was 110 per cent of average normal function; cultures of the urine sediment on different occasions developed isolated colonies of alpha hemolytic streptococcus, non-hemolytic *Staphylococcus albus*, and hemolytic *Staphylococcus aureus*. Intravenous pyelography resulted in adequate excretion of the dye and the shadows had normal outlines. The prostatic smears did not contain pus cells and cultures remained sterile. Beta hemolytic streptococci were not recovered from the throat. Wassermann and Kahn reactions were repeatedly negative. Agglutination for *B. abortus*, *S. dysentery* and *S. paradysentery* (W) could not be demonstrated. Stools failed to reveal any ova, parasites, or blood. Frei, brucellergin, PPD, and *H. ducrey* vaccine intracutaneous tests failed to evoke any skin reactions. Roentgenographic studies of the heart, the knees, the wrists and the ankles showed normal film patterns. On May 24 the EKG exhibited a P-R interval of .24 second and on June 4 an interval of .20 second. Thereafter until subject was last seen in August the duration of A-V conduction was persistently below .18 second (figure 2).

The P-R intervals varied as follows:

January 23, 194520 sec.
February 1, 194524
February 12, 194521
February 23, 194522
March 14, 194518
March 23, 194523
April 3, 194520
April 30, 194520



Jan. 23

Feb. 1

Feb. 12

Feb. 23

Mar. 14

FIG. 2.

SUMMARY

Two cases of Reiter's disease are presented in which abnormal prolongations in auriculoventricular conduction appeared. In neither case could an infectious etiologic agent be found.

BIBLIOGRAPHY

1. REITER, H.: Ueber eine bisher unerkannte Spirochäteninfektion (*Spirochaetosis arthritica*), Deutsch. med. Wchnschr., 1916, xlii, 1535-1536.
2. LEVER, W. F., and CRAWFORD, G. M.: Keratosis blennorrhagica without gonorrhoea (Reiter's disease?), Arch. Dermat. and Syph., 1944, vi, 389-397.
3. COLBY, F. H.: Renal complications of Reiter's disease, Jr. Urology, 1944, lii, 415-419.
4. BAUER, W., and ENGELMAN, E. P.: A syndrome of unknown etiology characterized by urethritis, conjunctivitis and arthritis (so-called Reiter's disease), Trans. Assoc. Am. Phys., 1942, lvii, 307-313.
5. a. BEIGLBÖCK, W.: Zur Behandlung der Reiterschen Krankheit (Rurrheumatismus), Deutsch. med. Wchnschr., 1943, lxix, 803-805.
b. Abstract of 5 a: Bull. War Med., Med. Research Council, 1944, iv, 653-654.
6. SHERMAN, W. L., BLUMENTHAL, F., and HEIDENREICH, J.: Blennorrhagic balanitiform keratoderma, Arch. Dermat. and Syph., 1939, xxxix, 422-429.
7. EPSTEIN, E., and CHAMBERS, S. O.: Keratosis blennorrhagica with corneal lesions, Arch. Dermat. and Syph., 1937, xxxvi, 1044-1051.

INTOXICATION RESULTING FROM THE ADMINISTRATION OF MASSIVE DOSES OF VITAMIN D, With Report of Five Cases *

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THE fact that massive doses of vitamin D may produce toxic symptoms and even death in man has been recognized for many years. It is only in the past few years, however, that the administration of this substance in massive doses has become popular with physicians and that the misinformation relative to its merits in the treatment of arthritis publicized by a certain widely read "digest" of current literature has induced some people to use it in self-medication. In the past year we have recognized the syndrome of vitamin D intoxication in five patients whose records are briefly reported later in this paper. Because these patients were very ill as a result of this intoxication, because the syndrome may easily be confused with other conditions, and because of the apparent increase in the number of these cases, it seems timely to discuss this subject.

In 1933 Rappaport and Reed ¹ treated a number of cases of allèrgic conditions with massive doses of highly potent viosterol. They found that this substance raised the blood calcium to very high levels, lowered the potassium level, diminishing its wide fluctuations, and stabilized the calcium-potassium ratio at a relatively low level. Certain of the patients under treatment showed toxic injury and they found that the threshold of toxicity varied in different individuals and sometimes in the same person at different times. They felt that the toxic symptoms were easily recognized and that they abated promptly on discontinuance of the drug or reduction in the amount administered.

In 1934, Wyatt, Hicks, Allen and Thompson ² reported the treatment of 40 cases of proliferative arthritis with vitamin D. They never administered over 300,000 international units per day and usually not over 200,000. They used irradiated ergosterol in sesame oil, viosterol, and vitamin D in propylene glycol. Twenty per cent of the patients had to discontinue this treatment because of toxic symptoms. They mention loss of appetite, drowsiness and slight headache as the more common symptoms, but in one of the eight cases showing toxic symptoms there occurred "violent persistent nausea, intense headache and sweating." They found that the calcium increase in the blood was from 0.75 to 0.95 mg. per 100 c.c. and that the calcium-phosphorus ratio was undisturbed.

In the same year Reed ³ reported on the symptoms of viosterol overdosage. He found that the first symptom of overdosage was frequency of

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urination. This symptom did not necessarily imply that the total output of urine was increased and it was not necessarily due to increased calcium excretion through the kidney. Urinary frequency was soon followed by nausea and vomiting and then, shortly, diarrhea. These symptoms abated in three to four days after the drug was stopped. Toxicity was always accompanied by loss of weight, which he felt was due to increased basal metabolic rate. The weight loss was accompanied by increased nitrogen excretion.

He states that toxicity is not synonymous with hypercalcemia. In comparing it with the effect of administration of parathyroid hormone he found that, with the hormone, a blood calcium level of 16 mg. per cent is dangerous, whereas with viosterol one subject had a blood calcium of 29 mg. per 100 c.c. of blood for two weeks without signs of toxicity and another maintained a level of 24 mg. for eight days with no toxic symptoms.

Reed concludes that one need not be apprehensive of doses up to 150,000 units per day for "indefinite periods," but it is interesting to note that Vrtiak and Lang,⁴ reporting on the treatment of 20 cases of chronic arthritis, using from 150,000 to 250,000 international units per day, said that "Nausea developed in all patients; in a few, frequency of urination and nocturia."

In 1937 Steck, Deutsch, Reed and Struck⁵ reported on their experimental studies regarding intoxication with vitamin D. This work was done on dogs. They point out that there is a species variation in susceptibility but that dogs and human beings are very much alike in this regard. The 64 dogs in their series received doses of vitamin D which would rarely, if ever, be approached in man. These doses ranged from one million units per kilogram per day down to less than 20,000 units per kg. per day. They all had marked elevation of blood calcium with a maximum of 21.6 milligrams per cent, marked weight loss and marked signs of intoxication. They all died in coma. The survival time with any dosage over 50,000 units per kg. per day averaged 12 days; with doses between twenty and fifty thousand units it averaged 39 days; and with less than 20,000 units, 68 days.

The objective symptoms were about the same as noted in the human subject, consisting of weakness and lassitude, anorexia, polydipsia, polyuria, psychic disturbances and diarrhea. Bloody feces were passed by 11 of the 64 dogs. In these, petechial hemorrhages were found in the mucosa of the stomach and intestines. In the most intense intoxications the premortal coma was a constant and characteristic feature. It was preceded by partial paralysis, slow shallow respirations, fine thready pulse, salivation and psychic changes whereby a previously tame and friendly dog was rendered unmanageable and vicious.

Autopsy was performed on each of these dogs. It was found that, of the 13 tissues selected for microscopic examination in each animal, the kidney proved to be the most vulnerable. Here, the first sign of damage was cellular degeneration. It was followed by the deposition of calcium in the damaged cells. There was great loss of fat, some of the animals being entirely devoid of it. These authors found that if the administration of the

drug was stopped early enough for the animal to survive, complete repair of the damaged tissues ensued, but that no animal or human being will recover so long as the medication is continued.

The increased excretion of calcium which takes place is not due to removal of the soft tissue deposits entirely, because it begins before there is any microscopic evidence of soft tissue deposits. It is thought to come from the trabeculae of the bone. The average level of calcium in the blood begins to fall after the output in the urine rises.

In addition to their experimental work, these authors collected data on the administration of vitamin D to 773 human cases. The dosage in these cases varied from 1,500 to 35,000 units per kilogram per day. A total of 63 cases, or 8 per cent, gave evidence of intoxication. Of these only two could certainly be said to have died of this intoxication.

They conclude that their experience indicates that "administration of massive doses of vitamin D should not be undertaken for any cause except under careful supervision of a physician who can and will carefully check the patient's condition at frequent intervals and who will see to it that the treatment is discontinued promptly on the appearance of the first signs suggestive of toxicity." They believe that any sign of kidney dysfunction is an absolute contraindication and that arteriosclerosis is probably a contraindication, therefore administration to older subjects should be undertaken "with extreme caution."

In this connection, Slocumb⁶ concludes from his experience in the treatment of infectious arthritis that ". . . there is some risk of renal damage, which is temporary if the administration of vitamin D is discontinued promptly after evidence of toxicity appears, but serious damage may occur." He calls attention to the fact that concentration of urea in the blood may rise in some of these cases of intoxication.

From this brief review of part of the existent literature it appears that vitamin D in massive doses bears no relationship in its action to the use of this drug in deficiency disease. It is a powerful and dangerous drug which should be used with caution at all times, and there are definite contraindications to its use in some individuals. It mobilizes calcium from the trabeculae of the bones and thus raises the blood calcium level. The excess is excreted largely through the kidney. It often produces cellular degeneration in various organs of the body, and this is most marked and obvious in the kidney. The degenerated cells become the repository for calcium. The fat tissue of the body is rapidly burned up until it may practically disappear. Nitrogen may accumulate in the blood, presumably owing to the inability of the damaged kidney to excrete it. That it produces other chemical changes, all of which may not yet be known, is shown by its effect on the blood potassium which is lowered and loses its natural property of rapid and marked fluctuation. It is also apparent that mild intoxication with this drug is probably harmless unless it be permitted to continue over a long period of time and that complete restitution of the injured tissues usually takes place.

The symptoms of intoxication are readily recognized and have been enumerated above. If they are encountered during the course of the administration of the drug, the attending physician can recognize them promptly and act accordingly. However, if the patient is not closely observed, or if he is treating himself, as did some of our cases, the symptoms of intoxication may go on for considerable periods of time without recognition and may presumably cause permanent injury or even death.

CASE REPORTS

Case 1. Mrs. E. A., white female, age 66, was treated for a chronic osteoarthritis involving numerous joints, and in increasing severity from 1933 to 1944. On Feb. 4, 1944, she came complaining of a great deal of pain from her arthritis. There was considerable tenderness over the spine, grating and limitation of motion of the knees, and tender, inflamed finger joints. The pulse rate was 84 and blood pressure 110 mm. Hg systolic and 70 mm. diastolic. Her general physical examination was not remarkable aside from the arthritic condition. On the day of examination she seemed to be less alert mentally than when last observed, but she seemed oriented and had travelled alone more than 50 miles to reach our offices.

Laboratory data on Feb. 4 revealed a normal urine with 1.023 specific gravity. The blood showed 12.5 gm. of hemoglobin with 4,160,000 red cells; 6,900 white cells and a normal blood picture. The sedimentation rate of the erythrocytes was 26 mm. in one hour. The blood Wassermann reaction was negative.

The patient expressed a desire to try massive doses of vitamin D, so she was given 50,000 unit capsules with instructions to begin with one daily and gradually increase to four capsules (200,000 units) daily. About two weeks later she complained of dizziness and stated that she had fallen several times. For this reason she was admitted to Lincoln General Hospital on March 13, 1944. She appeared apathetic and was disoriented. The general physical and neurological examination revealed nothing excepting a mild psychotic state and the old arthritic condition which had not improved under the vitamin D therapy. There was occasional incontinence of urine. The output per day could not be accurately measured but seemed to be increased. There was no nausea, vomiting or other gastrointestinal disturbance.

Laboratory data in the hospital showed a normal urine of specific gravity 1.025. The blood examination revealed 11.4 gm. of hemoglobin; 3,900,000 erythrocytes and 6,850 leukocytes per cu. mm. with a normal differential count. The urinary calcium was markedly increased and the blood calcium was 12.7 mg. per 100 c.c. of blood. The blood urea was 38 mg. per 100 c.c. One week later the urinary calcium was still increased. After two weeks without vitamin D the blood calcium had dropped to 11.8 mg. per 100 c.c. She was dismissed with but little change in the mild psychosis, but less tendency to ataxia upon standing and walking. We considered this to be a case of vitamin D intoxication with the somewhat unusual presenting symptoms of vertigo and tendency to fall and with at least an exaggeration of a tendency to senile psychosis.

Case 2. Mrs. J. B., a white female, age 54, was admitted to Lincoln General Hospital on Aug. 8, 1945 complaining of severe headache, nausea and vomiting of four weeks' duration with 16 pounds loss in weight. She had had painful and swollen joints, the knees, feet and hands being chiefly involved, for the past eight years. For this arthritic condition she had been taking vitamin D, 200,000 units daily for the first 30 days and 350,000 units daily for the next 60 days just preceding admission to the hospital. She stated that her arthritis had definitely improved. Physical examination showed nothing remarkable and no evidence of arthritis except some tenderness over the spine. Blood pressure was 160 mm. Hg systolic and 90 mm. diastolic.

Laboratory data on admission showed a urine of 1.012 specific gravity with albumin 2 plus and occasional hyaline and granular casts. The blood examination revealed a negative Wassermann reaction; a sedimentation rate of the erythrocytes of 23 mm. in one hour; 12 gm. of hemoglobin; 3,600,000 erythrocytes, 10,300 leukocytes per cu. mm., and a normal differential count. The blood urea was 80 mg. per cent, the blood creatinine was 3 mg. and blood calcium, 11.5 mg. per 100 c.c. of blood. One week later the blood urea had dropped to 50 mg. per 100 c.c. The urinary calcium was still increased.

At the time of discharge from the hospital she had no headache, her arthritis was in good condition, and her blood pressure was 180 mm. Hg systolic and 90 mm. diastolic. One month later there was a recurrence of the arthritis but there was no vomiting and only slight headache. Blood pressure was 180 mm. Hg systolic and 110 mm. diastolic. The urine showed a specific gravity of 1.012, only a trace of albumin and occasional hyaline casts and cylindroids. The blood urea at that time had dropped to 33 mg. per 100 c.c.

Case 3. Mrs. P. S., a white female, age 45, was admitted to the Lincoln General Hospital on Sept. 3, 1945 complaining of cramping pains in the legs for one week and a severe nocturnal headache for three days (previously she rarely had headaches). Because of a mildly painful joint in her right hand of two years' duration she had been taking 50,000 unit vitamin D capsules for the past year. She started with one capsule, then increased one capsule daily up to eight, then reduced one each day down to one capsule daily and then repeated the same cycle again and again. For the past six months she had thus taken an average daily dose of 225,000 units. There had not been any change in the very mild arthritis. Four months before admission she had some polydipsia and polyuria with a heavy sediment noted in the urine. These symptoms lasted for one month. This had recurred two months before admission with some burning on urination. Physical examination showed nothing remarkable excepting some redness and injection of the sclera. The only evidence of arthritis was slight tenderness of one interphalangeal joint. The blood pressure was 185 mm. Hg systolic and 105 mm. diastolic.

Laboratory data revealed a urine of 1.010 specific gravity containing albumin 1 plus but otherwise negative. The blood Wassermann reaction was negative. The sedimentation rate of the erythrocytes was 27 mm. in one hour. The blood contained 10.8 gm. of hemoglobin per 100 c.c., 3,930,000 red cells and 11,800 white cells per cu. mm. with a normal differential count. The blood urea was 61 mg. and blood calcium 13 mg. per 100 c.c. The phenolsulfonphthalein kidney function test returned 8 per cent of the dye in 15 minutes, 9 per cent the next 45 minutes, and 2 per cent the second hour, a total of 19 per cent in two hours.

About one week after discontinuance of vitamin D the patient looked and felt much better. The blood urea had dropped to 37 mg. per 100 c.c. The urea clearance was only 38 per cent of the normal and the specific gravity of the urine remained low. The blood pressure was 150 mm. Hg systolic and 90 mm. diastolic. About one month later the blood pressure was found to be 135 mm. Hg systolic and 85 mm. diastolic, she felt much better with only a slight morning headache and the scleral injection had entirely disappeared.

Case 4. Mrs. J. H., a white female, aged 68, had been treated for arteriosclerosis and hypertension for several years. Her blood pressure ranged from 166 mm. Hg systolic and 100 mm. diastolic to 208 mm. Hg systolic and 112 mm. diastolic. Following a sprained ankle and fracture of her right arm in 1944, she developed marked arthritis with stiffness, redness and swelling of her wrists, knees, ankles, hips and shoulders. In July 1945 she was given 50,000 unit vitamin D capsules with instructions to take one daily for one week, then to increase the dose to two capsules daily. She, however, continued to increase the dosage each week until in October she was

taking seven capsules daily (350,000 units). At that time she complained of vertigo, nausea and vomiting. The urine showed a specific gravity of 1.011, a moderate number of pus cells, many hyaline casts and cylindroids, and a few granular casts. The urinary calcium was slightly increased. Her blood pressure was the lowest ever recorded, 156 mm. Hg systolic and 90 mm. diastolic. The arthritis had improved somewhat.

Two weeks after all vitamin D had been discontinued she felt much better, the appetite was good and there was very little vertigo. The urinary calcium was not increased and the blood urea was 20 mg. per 100 c.c. of blood.

Case 5. Mr. M. G., a white male, age 29, had tuberculosis of the spine when five years of age with a marked dorsal kyphosis. When 24 years of age he had a cold abscess in the back and left thigh. The present illness dated back two weeks when he vomited for several days which was very unusual for him. He was again vomiting when first seen on March 6, 1945 and had lost about 10 pounds in weight. He stated that four months before he had had some back and sciatic pain which had improved upon receiving some vitamin B injections which he had continued to take occasionally since that time. He said that he was taking no other medicine. Physical examination was essentially negative except for the severe dorsal kyphosis which reduced the longitudinal diameter of the abdomen by about 50 per cent. The blood pressure was 126 mm. Hg systolic and 94 mm. diastolic.

Laboratory data revealed a negative Wassermann reaction, a sedimentation rate of 20 mm. in 1 hour, 13 gm. of hemoglobin per 100 c.c. of blood, 4,710,000 erythrocytes, 7,050 leukocytes per cu. mm. and a normal blood picture. The urine had a specific gravity of 1.011 with a few leukocytes. In rechecking the urine on the same day, many cylindroids were found. During the next few weeks, repeated urine examinations showed a trace of albumin, many hyaline casts and cylindroids and occasional granular casts. The phenolsulfonphthalein test returned 16 per cent of the dye in 15 min., 12.5 per cent in the next 45 min. and 12.2 per cent in the second hour, a total of 40.7 per cent. The blood urea was 66 mg. per cent. Roentgen-ray examination of the gastrointestinal tract was negative.

After several days of vomiting he again felt fine for two weeks, when the nausea and vomiting recurred. This same cycle recurred for the third time when it was discovered that he had been taking from one to eight 50,000 unit capsules of vitamin D daily for the past four months. When he vomited, he had to stop the vitamin D but would take it again as soon as he could eat. The urine was then examined for calcium which was not found to be increased, but the blood calcium was 12.5 mg. per 100 c.c.

After stopping the vitamin D, his appetite was again good and he felt well. After 20 days the blood calcium was down to 10.6 mg. and the blood urea, to 49 mg. per 100 c.c. Two weeks later (over one month after stopping the ingestion of vitamin D) the urine showed no albumin, no increase in calcium, and only a few hyaline casts and cylindroids; but the blood urea had again risen to 60 mg. with a hemoglobin of 8 gm. per 100 c.c. of blood.

It seems probable that the kidney damage was severe enough so that full restitution may be impossible and secondary hypochromic anemia has developed.

The treatment in all of these cases consisted of:

1. Discontinuing the administration of vitamin D.
2. Forcing fluid intake.
3. Administration of vitamin B in large doses—usually by parenteral injection.
4. A restricted protein diet for a short time in some cases.

DISCUSSION

In four of five of these cases ranging in age from 29 to 68 years vitamin D was taken in dosage larger than is considered safe, namely 150,000 units per day. Two of the five cases were victims of arteriosclerosis and hypertension, conditions which have been said to contraindicate the use of this drug. In two cases the dosage was increased voluntarily by the patient much beyond the amount ordered by the physician. In case 1 the mental status of the patient, while not obviously psychotic, was known to have deteriorated in comparison with previous observations. At our last observation the psychosis was obviously worse than before taking vitamin D. Although this condition has not been mentioned as a contraindication to massive doses of vitamin D, the moderate dosage she received, 200,000 units per day, seems to have increased her psychic disorder. This effect has been noted in dogs as stated earlier in this paper. It is possible that psychic disorders, especially in the aged, should be considered as a contraindication to the use of this substance in massive dosage.

The most common symptoms were nausea, vomiting and headache. Associated with these symptoms there was a group of findings indicating renal injury and consisting of albuminuria of moderate grade, the presence of granular casts, an elevation of blood urea and a depression in the output of phenolsulfonphthalein.

Blood calcium was slightly increased in the four cases in whom it was estimated and there was generally an increase in urinary calcium but this was noted as marked in only one instance.

A moderate normochromic anemia was found in three of the five cases and slight leukocytosis, in two.

CONCLUSIONS

1. Vitamin D in massive doses is a toxic substance which produces parenchymal injury especially in the kidney.

2. In doses greater than 150,000 units per day, it is a dangerous drug.

3. In individuals who have evidence of renal disease it should not be used.

4. In those with hypertension and signs of arteriosclerosis and those who show any signs of psychic disturbance its safe use is open to question.

5. In any individual the use of this substance should be frequently and carefully supervised. The discontinuance of the drug at the first sign of intoxication will usually cause the prompt disappearance of symptoms and, probably, the restitution of the injured tissues.

6. Injury to parenchymatous organs, especially the kidney, may progress to the point where restitution is impossible, as seems to be true in our case 5.

BIBLIOGRAPHY

1. RAPPAPORT, B. Z., and REED, C. D.: Viosterol of high potency in seasonal hay fever and related conditions, *Jr. Am. Med. Assoc.*, 1933, ci, 105.

2. WYATT, B. L., HICKS, R. A. and THOMPSON, E. E.: Massive doses of vitamin D in the treatment of proliferative arthritis, *Ann. Int. Med.*, 1934, x, 534.
3. REED, C. I.: Symptoms of viosterol overdosage in human subjects, *Jr. Am. Med. Assoc.*, 1934, cii, 1745.
4. VRTIAK, EMIL G., and LANG, ROSS S.: Observations on the treatment of chronic arthritis with vitamin D, *Jr. Am. Med. Assoc.*, 1936, cvi, 1162.
5. STECK, I. E., DEUTSCH, H., REED, C. I., and STRUCK, H. C.: Further studies on intoxication with vitamin D, *Ann. Int. Med.*, 1937, x, 951.
6. SLOCUMB, C. H.: Vitamin D in the treatment of infectious arthritis, *Ann. Int. Med.*, 1942, xvi, 241.

CASE REPORTS

FRIEDLÄNDER PNEUMONIA TREATED WITH STREPTOMYCIN; REPORT OF A CASE WITH PROMPT RECOVERY *

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THE introduction of streptomycin has provided a new antibiotic effective against many Gram negative organisms unaffected by penicillin. The Friedländer bacillus (*Klebsiella pneumoniae*) has been shown to be susceptible to streptomycin in vitro,¹ but the effect of this agent on acute Friedländer pneumonia is not known.† Recently, the opportunity arose for just such a therapeutic trial. The patient responded so rapidly to streptomycin that a report was felt justified, especially since this type of pneumonia is so refractory to other drugs.

CASE REPORT

The patient, a 36 year old white infantry soldier, sustained a penetrating shell fragment wound of the right forearm on December 15, 1944, in France. Three days after injury the fingers of the right hand began to turn black. Dorsal sympathetic blocks were performed, but by the tenth day the fingers were completely black. He was then evacuated through channels to the zone of the interior. The soldier complained of severe pain in the arm and forearm, and on February 19, 1945 a dorsal sympathectomy was performed with immediate relief of much of the discomfort in the extremity. The forearm wound continued to drain, and culture obtained on February 26, 1945 disclosed "bacilli of the mucosus encapsulatus group." A later culture on March 17 disclosed only *B. subtilis* and *B. proteus*. On March 2 the gangrenous portion of the fingers was removed. He subsequently developed an abscess of the right hand which was drained on May 29, 1945. On July 26, 1945 he was transferred to this plastic surgery center and on arrival the forearm wound was healed, but slight drainage persisted in the amputated stump of the right index finger. During the period from February until May 1945, he received penicillin, 20,000 units intramuscularly every three hours, almost continuously.

On October 3, 1945 a revision of the stumps of the right index and middle fingers was performed under general inhalation anesthesia. On October 8 the middle finger stump was practically healed, and the index finger stump was healing satisfactorily. The surgeon stated that there was no active infection. On the evening of October 10 he developed sharp pain in the lower left chest posteriorly and in the left axilla. Examination of the chest at that time showed nothing remarkable and there was no fever. However, the next day the pain persisted and temperature rose to 100° F. A slight unproductive cough appeared. On October 12 a medical consultation was requested.

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† At the time this report was submitted we were not familiar with the paper of HERRELL, W. E., and NICHOLS, D. R.: The clinical use of streptomycin: A study of 45 cases, Proc. Staff Meetings, Mayo Clin., 1945, xx, 449, in which the authors described two cases of Friedländer pneumonia treated with streptomycin.

On examination the patient was obviously uncomfortable, although he did not appear seriously ill. Motion of the left chest was markedly restricted. The percussion note was dull at the left base and low in the left axilla. Breath sounds were diminished in these areas, but no râles were audible. A coarse friction rub was present just below and medial to the left scapular angle. It was felt that the patient had an early left lower lobe pneumonia, although the possibility of pulmonary infarction was entertained because of a history of thrombophlebitis in the right leg one year previous with a minor recurrence in August 1945. Chest roentgenogram on October 12 disclosed a faint area of consolidation in the axillary portion of the left lower lobe with slight elevation of the left diaphragm. The left costophrenic angle was slightly hazy, but no free fluid appeared to be present. Blood count disclosed 10,550 leukocytes of which 71 per cent were polymorphonuclear neutrophils. Sputum cultures was obtained, and penicillin therapy was instituted on October 12 (40,000 units intramuscularly every three hours).

**Friedländer's Pneumonia (*Kl. pneumoniae* Type A)
Treated with Streptomycin**

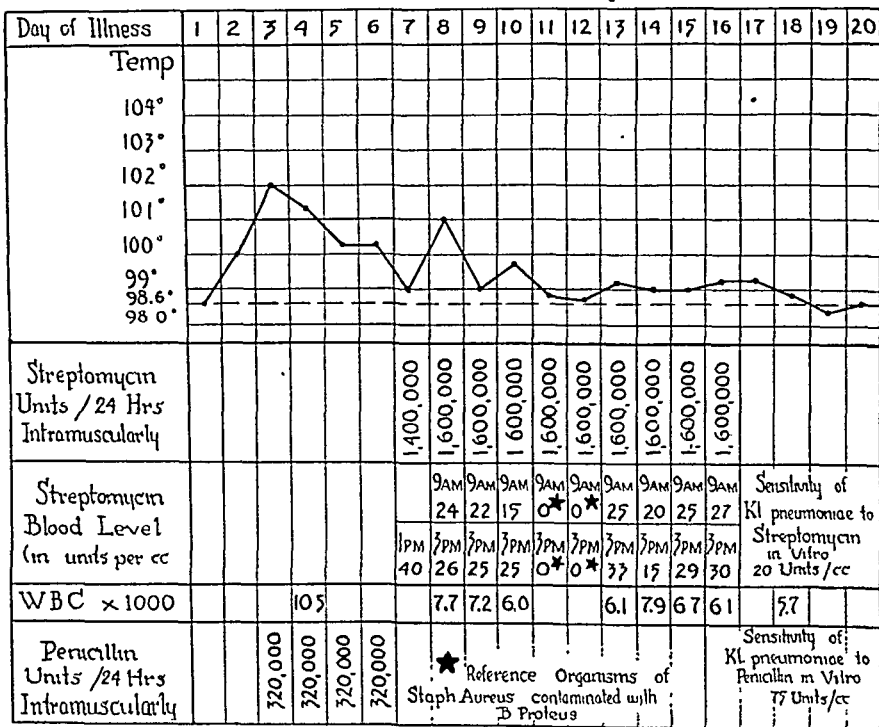


FIG. 1.

Because of the severe pleuritic pain, the left chest was strapped with adhesive. On October 13 there was no change in the patient's condition. He continued to complain of severe pain in the left axilla and the physical signs were the same. On October 14 his fever had fallen somewhat and he began to cough up small quantities of tenacious, frankly bloody, sputum. Examination of the chest disclosed a greater area of dullness at the left base and in the left axilla. A second roentgenogram on October 15 showed increase in the consolidation. The lateral portion of the involved lower lobe appeared very dense while the medial portion showed only mottled density. Also noted was moderate pleural thickening over the right apex. Sputum culture report on October 15 was "Friedländer bacillus (*Kl. pneumoniae* type A), 4 plus." Neufeld

typing for pneumococci was negative. On October 16 the patient still appeared acutely, but not seriously, ill. The signs of consolidation were more extensive over the left lower lobe. There was increased vocal resonance over the involved area but the breath sounds were still diminished. Despite the fact that the temperature was falling the patient was clinically worse. It was decided to institute streptomycin therapy since reports indicate that Friedländer bacillus is insusceptible to penicillin.² Accordingly, at noon on October 16 penicillin was discontinued and streptomycin begun in doses of 200,000 units intramuscularly every three hours. A second sputum culture, obtained just before this change in therapy, again revealed Friedländer bacillus (*Kl. pneumoniae* type A) 4 plus. The sensitivity of this organism to streptomycin was determined and found to be 20 units/c.c. of an F.D.A. broth culture. Streptomycin blood levels were determined at 9 a.m. and 3 p.m. daily by the method of Stebbins and Robinson.³ Unfortunately a blood culture was not obtained until about 18 hours after streptomycin therapy was begun, and this was negative. The patient made rapid improvement, and sputum cultures obtained on October 17 and daily thereafter were negative for Friedländer bacillus. He continued to cough up tenacious bloody sputum for three days, but by October 18 there was return of resonance and increase in breath sounds at the left base. The hand wounds appeared clean and there was no drainage. By October 20 the temperature was normal and remained so. The patient tolerated the streptomycin well and there were no untoward reactions, except soreness locally at the site of injection. Chest roentgenogram on October 21 disclosed considerable clearing in the density at the left base. A shadow persisted in the axillary portion of the left lung. Near the superior and medial margin of this shadow there was a small area of translucency which could possibly represent a small cavity, although the appearance was not at all definite. On October 25, after the temperature had been normal for six days, the streptomycin was discontinued. The patient then made an uneventful recovery. Chest roentgenogram on October 31 revealed still further clearing of the density in the left lower lung field. The left diaphragm was in normal position, but there were definite diaphragmatic adhesions in the mid-portion producing some tenting. Another roentgenogram on November 9 showed only slight haziness in the axillary portion of the left lower lung field and persistence of the diaphragmatic adhesions. A final roentgenogram on November 21 disclosed no residual parenchymal lesion. The left diaphragm was elevated and there was evidence of pleural thickening in the region of the interlobar fissure.

The fact that bacilli of the *mucosus encapsulatus* group were recovered from the forearm wound on February 26, 1945, was unfortunately not discovered until the patient had completely recovered from the pneumonia. By this time all wounds were well healed and no material for culture was available.

COMMENT

The Friedländer bacillus (*Kl. pneumoniae*) is the etiologic agent in a small but definite percentage of lobar pneumonia cases. Julianelle⁴ described three serologic types, A, B, and C, and a mixture X, type specificity depending on capsular polysaccharide. Type A was the responsible agent in 74 per cent of one series of 45 cases of Friedländer pneumonia.⁴ The disease may lead to early death, recovery in a relatively small percentage, or chronic suppurative pulmonary disease with abscess formation. The mortality is high. Solomon⁵ reported deaths in 97 per cent of 32 cases receiving no chemotherapy. Perlman and Bullowa⁶ found that sulfanilamide, sulfapyridine, or type specific serum, or combinations of these were of little value. Hyde and Hyde⁷ state that the value of chemotherapy is not clear, but that sulfonamides are of some value in human

Friedländer pneumonia in the early stages. Anderson,² in a review of penicillin therapy, lists the Friedländer bacillus among a group of organisms that are not adversely affected by concentrations of penicillin that can be achieved in the blood or tissues. He points out, however, that several relatively insusceptible organisms can be inhibited *in vitro* by use of relatively high concentrations of penicillin, indicating that penicillin insensitivity is a relative quality. This is demonstrated in the case here reported. Penicillin sensitivity studies *in vitro* disclosed that a concentration of 75 units of penicillin per c.c. was necessary to inhibit the growth of this strain of *Kl. pneumoniae*. Levels approaching this are never approximated in penicillin therapy. It can be argued that such levels are not necessary *in vivo*, since the action of penicillin in human infections is bacteriostatic—that the actual destruction and elimination of the infecting organisms are probably effected by the normal defense mechanisms of the host.² We thought this at first to be the case in our patient, since his temperature began to fall while he was receiving penicillin. However, since there was spread of the pneumonic process, and since the sputum cultures still showed the presence of the organisms, streptomycin therapy was decided on. The response was prompt, and the sputum cultures were consistently negative after two days of treatment. It is of interest that sensitivity studies *in vitro* disclosed 20 units of streptomycin per c.c. of F.D.A. broth culture to inhibit this strain of *Kl. pneumoniae*, and that such levels were attained in the blood by the dosage of streptomycin employed.

An unusual feature in this case was the presence of "bacilli of the mucosus encapsulatus group" (probably *Kl. pneumoniae*) in the culture of the forearm wound on February 26, 1945. Since there were small draining areas in the finger stumps at the time of the plastic procedure on October 3, 1945, it appears most likely that Friedländer bacilli were present in the wounds of the hand, and that the operation resulted in low grade bacteremia culminating in the pneumonia. Unfortunately, a blood culture was not obtained until 18 hours after the institution of streptomycin and this was negative.

SUMMARY

A case of Friedländer pneumonia caused by *Kl. pneumoniae* type A is described, which was successfully treated with streptomycin after apparent failure of penicillin. It is appreciated that the treatment of a single case does not establish the value of a new therapeutic agent. However, the rapid recovery from a disease ordinarily so refractory to other known methods of treatment should indicate the further trial of streptomycin in Friedländer pneumonia.

We are grateful to Lieutenant F. V. Lucas, Sanitary Corps, Army of the United States, for the bacteriologic studies including sensitivity determinations and streptomycin levels.

BIBLIOGRAPHY

1. Unpublished data, Merck and Co., Inc., Rahway, N. J.
2. ANDERSON, D. G.: The treatment of infections with penicillin, *New England Jr. Med.*, 1945, ccxxxii, 400.
3. STEBBINS, R. B., and ROBINSON, H. J.: A method for determination of streptomycin in body fluids, *Proc. Soc. Exper. Biol. and Med.*, 1945, lix, 255.
4. JULIANELLE, L. A.: A biological classification of encapsulatus pneumoniæ (Friedländer's bacillus), *Jr. Exper. Med.*, 1926, xlv, 113.

5. SOLOMON, SAUL: Primary Friedländer pneumonia; Report of thirty-two cases, Jr. Am. Med. Assoc., 1937, cviii, 937.
6. PERLMAN, ELY, and BULLOWA, J. G. M.: Primary bacillus Friedländer (*Klebsiella pneumoniae*) pneumonia; therapy of *B. Friedländer* B pneumonia, Arch. Int. Med., 1941, lxxvii, 907.
7. HYDE, LEROY, and HYDE, BERNARD: Primary Friedländer pneumonia, Am. Jr. Med. Sci., 1943, ccv, 660.

HEMATOPORPHYRINURIA: REVIEW OF LITERATURE AND REPORT OF A CASE OF CHRONIC TYPE*

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PORPHYRINS are chemical compounds participating in the normal pigment metabolism and occurring throughout the plant and animal worlds. They are of special interest in medicine because of their occurrence in hemoglobin, in bile-pigments, in chlorophyll, and in the widely distributed coloring matter, cytochrome. All porphyrins have a common chemical structure, namely four pyrrole rings bound by four additional carbon atoms, and are able to form compounds with metals. In the blood pigment the porphyrin is called protoporphyrin and this combined with iron and the protein fraction, globin, forms the basis for hemoglobin.

The organism receives the porphyrin either directly or by transformation of the chlorophyll, the hemoglobin, or the myoglobin in the gastrointestinal tract. This transformation probably takes place through the action of intestinal bacteria. Part of the porphyrin is absorbed by the intestine and conducted to the liver where it is changed to bilirubin or to other forms of porphyrin; part of it enters the circulation and is carried either to the organs of storage or to the kidneys where it is excreted. In addition to this, production of porphyrin takes place in the reticulo-endothelial system, especially in the liver cells, during the course of the transformation of hemoglobin to bilirubin, and it also takes place in the bone marrow during the synthesis of the blood pigment. Pathologic porphyrinuria may therefore be the result of disturbances in any of the organs participating in the pigment metabolism.

Two porphyrins appear to be the most important in cases of pathologic porphyrinuria, namely, (1) coproporphyrin which occurs in normal feces, and (2) uroporphyrin which is found in small quantities in normal urine. These two porphyrins, as they occur normally in excreta, are probably derived from plant and animal tissues taken as food. In certain pathological conditions both uroporphyrin and coproporphyrin are produced in excess in a manner as yet unknown and excreted in the urine and feces. Günther,⁶ who did the pioneer work in this field, believed that the disease represents a constitutional anomaly of pigment metabolism in the form of a reversion to an embryonic type. This he based on the fact that the embryo's red cells contain uroporphyrin as well as hemoglobin

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and that thus far no satisfactory evidence has been found that these porphyrins are derived from the breakdown of hemoglobin. Subsequent investigations, especially those indicating that porphyrias are a familial disease, tended to confirm Günther's original idea that the disease is caused by an inborn error of porphyrin metabolism.

From the etiologic point of view the porphyrias have been classified into congenital, acute, and chronic forms. The acute form has been further subdivided into acute toxic and acute idiopathic porphyria.^{1, 9} In regard to the acute toxic and the acute idiopathic forms, Watson and others^{11, 8} pointed out that these two forms probably represent the same condition and that they are indistinguishable either clinically or by laboratory procedures. The acute toxic form of porphyria is recognized only by the demonstration of a toxic agent, usually a barbiturate or a sulfonamide, which apparently are etiologic factors.³ Anxiety, exhaustion and infection are also given by some authors, notably Eldahl,² as precipitating factors for the acute toxic form. On the other hand, the acute idiopathic porphyria, it is assumed, is also produced by some toxic agent, which has not been identified.

Clinically the congenital form, which is rare and inherited as a recessive Mendelian characteristic, is featured by (1) the color of the urine, (2) the pigmentation of the teeth and bones, and (3) the sensitivity of the skin to light. The urine varies from a pink to a red or black color and often darkens after exposure to light (so-called photo-oxidation). The porphyrins found in the urine are coproporphyrin and uroporphyrin. There is a brown to pink pigmentation of the enamel of the teeth, and the bones of the hand may develop a brown pigmentation which may become so deep that it is visible upon transillumination. The skin lesions, which vary from simple erythema to vesicle formation and large bullae filled with a colorless or blood-stained fluid, are caused by the sensitivity of the skin to ultraviolet light. This skin sensitivity is usually evident in childhood and affects mainly the hands, neck and face. Healing leaves permanent scars and in some cases a brownish pigmentation of the original lesions. Although the condition continues through life and can be warded off as long as precaution against excessive sunlight is taken, Garrod⁴ thinks that the prognosis must be guarded since in these cases there is a great tendency toward the development of a very fulminating type of pulmonary tuberculosis.

Both the acute toxic and the acute idiopathic forms of porphyria are more common in women than in men.⁵ The condition may be familial and then is inherited as a dominant Mendelian characteristic. In women, according to Günther,⁶ it is very often associated with menstrual disorders. The symptoms of acute porphyria of either type include, (1) the voiding of red urine (port wine color) or brownish urine which may become red after exposure to light, (2) various types of gastrointestinal disturbances and abdominal pain, such as nausea, constipation, vomiting, (3) various abnormalities of the nervous system, as evidenced by psychotic manifestations or paralysis, usually of the ascending (Landry) type, (4) jaundice, (5) renal damage and (6) very rarely pigmentation of the skin or dermal photosensitivity. During the attack the urine usually contains a mixture of coproporphyrin and uroporphyrin. The central nervous system involvement and the psychic disturbances usually occur only in the acute toxic form, and if these symptoms are present, the prognosis is considered very poor, the mortality rate in these cases being about 75 per cent. The leading symptoms

in the acute idiopathic form are intermittent attacks of voiding port-wine colored urine. These attacks last from one to three weeks, and then the porphyrin usually disappears from the urine until the onset of a subsequent attack. In these cases there is often evidence of hepatic dysfunction, such as positive urinary reactions for urobilin and urobilinogen and intermittent attacks of mild jaundice. The pathologic changes in the fatal cases are chiefly in the nervous system and consist of degenerative changes in the peripheral nerves, the spinal cord, and the ganglia of the autonomic nervous system, especially those of the abdominal viscera. Presumably, the latter changes are responsible for the abdominal symptoms.

The chronic form contains those cases which do not fall into the two previous groups. This type runs a more protracted course and may have acute exacerbations, during which there usually is a heavy urinary excretion of porphyrin, which gives the urine a dark color. Usually the gastrointestinal symptoms, such as cramps, vomiting and constipation predominate, and frequently there is light sensitivity, though not as pronounced as in the congenital group. Nervous depression has also been observed occasionally. The chronic form may follow the prolonged use of barbiturates, especially sulfonal, trional, and veronal, even in ordinary dosage. Prognosis is somewhat better in this group than in the acute toxic group, but recovery is usually slow, and in rare instances this type has also proved to be fatal.

The diagnosis of porphyrinuria of any type depends upon the history, the clinical picture and the laboratory data, especially the examination of the urine. It is of great importance to recognize and confirm this condition because failure to do so, according to Geissler,⁵ "often misled to surgical interventions, because a diagnosis of intestinal obstruction, peptic ulcer, gallstone disease, renal calculi or appendicitis was made. Also hysteria or malingering has been assumed on account of negative organic findings." In the urine, the demonstration of uroporphyrin by spectroscopic examination is pathognomonic for this disorder. According to Nesbitt and Watkins⁹ patients with acute porphyrinuria usually excrete uroporphyrins III and I in the urine with a great predominance of the type III isomer, and only small amounts of coproporphyrin III and no uroporphyrin in the feces. Occasionally great difficulties may be encountered in demonstrating the characteristic spectroscopic bands of uroporphyrin, because this substance may be excreted as a metal complex. This difficulty, however, can be overcome by first treating the urine with acid. Another diagnostic test of value is the exposure of the urine to filtered ultraviolet rays. A pink fluorescence develops if porphyrins are present.¹

As far as the treatment of the porphyrias is concerned, nothing of a specific character has been found, since the cause of the disorder still remains unknown. Among therapeutic measures which prevent the excretion of porphyrins, liver extract and vitamins B and C have been mentioned with varying results.^{7, 10} The intravenous use of calcium has also been reported as improving the manifestations of the acute porphyrias.¹ In the congenital type exposure to sunlight should be avoided and the skin lesions be protected from secondary infections, while in the chronic type the offending agents, such as barbiturates and sulfonamides should be discontinued. The same naturally holds true for the acute toxic type, where the offending agent should be eliminated at once. Otherwise the treatment is purely symptomatic and supportive.

The following case is reported because of the diagnostic difficulties it presented. The failure to recognize this condition led to several major surgical operations and at one time to the somewhat vague diagnosis of psychoneurosis.

CASE REPORT

The patient, a 37 year old American-born housewife, was admitted to the hospital because of repeated attacks of voiding dark red urine, abdominal pain followed by diarrhea, nervousness and a slight yellowish tint of her skin.

She had had intermittent attacks of voiding red urine for the preceding 14 years and had consulted several physicians. The present admission was her fifth to a hospital. The first admission to a hospital was 14 years previously when she was treated for pyelitis and essential hematuria. At that time she also had intermittent abdominal pain, which was thought to be due to a chronic appendicitis. For this reason an appendectomy was performed. However, her abdominal pains as well as the attacks of voiding red urine persisted, and two years later she again was operated on, this time for a cystic right ovary which was believed to be the source of her abdominal pains. Following this, the abdominal pains disappeared for a while, but the attacks of voiding red urine persisted. These attacks occurred about two or three times a year and lasted for about one week. During these attacks there was a history of frequency, dysuria and nocturia, which were not present during the free intervals. Just prior to these attacks, it was noticed that the patient became very nervous and depressed. She also had slight abdominal pain, nausea and diarrhea during the attacks. Five years following her second hospital admission she was again admitted because of the increasing frequency of these attacks which were now accompanied by low back pain. At that time a complete and thorough genito-urinary study was performed, which included both retrograde and intravenous pyelograms. The urine examinations were entirely negative, no red blood cells being present in spite of the red color of the urine. Guinea pig inoculations with the urine proved to be negative for tuberculosis. The retrograde and intravenous pyelograms were normal and chest roentgenogram was negative for tuberculosis. The possibility of hyperthyroidism was also considered at that time, but the basal metabolic rate was within normal limits. However, following her discharge from the hospital, the attacks of voiding red urine continued and it was noted that her depressed mental states, as well as the attacks of abdominal pain, increased both in frequency and in severity. At that time, too, her skin started to become slightly yellowish in color. Because of that she again entered the hospital two years later, and this time a right nephrectomy was performed. The pathologic report of the removed kidney both macroscopically and microscopically was entirely negative. After her recovery and discharge from the hospital, she again started to void red urine and the yellowish tint of her skin increased gradually but steadily and finally reached a point where there was frank clinical jaundice present. At the same time her abdominal symptoms continued and there also was some tenderness in the upper right quadrant. She was not able to retain any food. There also was diarrhea. These symptoms persisted and the attacks of voiding red urine recurred at three to four month intervals. Because of jaundice and the abdominal symptoms she again entered the hospital where a cholecystectomy was performed. However, the pathologic examination of the gall-bladder was negative and no stones were found. She made a good recovery from the operation but her abdominal symptoms, such as diarrhea, nausea and vomiting, as well as the slight icteric color of her skin and the attacks of voiding red urine coupled with a depressed mental state persisted, so that at one time, since no objective organic findings could be detected, a diagnosis of psychoneurosis was made. All these symptoms continued until her present admission.

At no time during her long illness was there any history of prolonged or excessive

use of barbiturates or sulfonamides, she did not have any skin discolorations except jaundice, and there also was no evidence of any dermal photosensitivity. The menstrual history revealed that she had always had severe dysmenorrhea and that she already was experiencing menopausal symptoms before her oöphorectomy. She had been married for 18 years but never became pregnant.

The only pertinent factor in the family history was that patient's father died at the age of 66 years of "kidney trouble," the exact nature of which she was unable to recall. However, patient stated that her father prior to his death had similar attacks of voiding dark red urine. These attacks lasted for a few weeks and then disappeared spontaneously.

Physical examination on present admission revealed an underdeveloped and somewhat undernourished white female of the asthenic type. She appeared very restless, apprehensive and somewhat depressed mentally. The skin showed a slight icteric tint, and the mucous membranes were somewhat pale. No enlarged lymph nodes were palpable, and the thyroid gland appeared to be normal. Heart and lungs were normal. There was rather diffuse tenderness of the abdomen, with some localization over the right upper quadrant. The liver was enlarged and palpable three fingers' breadth below the right costal margin. The liver was soft but tender on palpation. The neurologic examination was entirely negative. Blood pressure was 110 mm. Hg systolic and 70 mm. diastolic.

The laboratory examinations were as follows: The urine was dark red in color with specific gravity ranging between 1.018 and 1.026. It contained some granular casts, bacteria and a few pus cells. No red cells nor hemoglobin were detected in any of the urine specimens. The red blood cell count varied between 3,790,000 and 5,130,000 with the hemoglobin values between 80 per cent and 95 per cent (Sahli method). White cell count was between 6,500 and 7,700 with a normal differential count. Examination of the blood smear showed nothing of significance. Wassermann and Hinton tests were negative. The sedimentation rate was 12 mm. in one hour (Wintrobe method). Blood culture and culture of the urine showed no growth, and guinea pig inoculation of urine was negative for tuberculosis. The fasting blood sugar was 96 mg. and the non-protein nitrogen was 30.5 mg. per 100 c.c. The Quick prothrombin time was 22 seconds. Stool examination was negative for occult blood. The concentration of proteins was 6.5 gm. per 100 c.c. of serum, the albumin being 4.0 and the globulin 2.5. Roentgenograms of the chest were negative, and the basal metabolic rate was minus 4 per cent.

The port-wine color of the urine deepened on exposure to light, and the characteristic fluorescence of porphyrinuria was observed when the urine was placed under ultraviolet light and was even noticeable when a test tube of urine was viewed in direct sunlight. Spectroscopic examination of the urine showed the characteristic absorption bands for uroporphyrin as the zinc metal complex.

Her clinical course while in the hospital was characterized by several episodes as previously described during which times her urine, otherwise normal in appearance, became dark brown or reddish-brown in color. Abdominal symptoms such as nausea, vomiting and diarrhea were also present, and at times there was diffuse tenderness over the entire abdomen. The jaundice varied from a very minimal degree to frank clinical icterus. There also was excessive sweating, mainly at night. There was no fever at any time.

Treatment in this case consisted of general supportive measures and specifically of plasma and whole blood transfusions, following which the attacks of voiding red urine seemed to stop momentarily, but only to return again later. She was also given both vitamin B and vitamin C in large doses intramuscularly and by mouth, but this too seemed to have only slight temporary effect on her condition and the attacks of voiding red urine as well as the abdominal symptoms recurred at intervals.

SUMMARY AND CONCLUSIONS

A case of chronic porphyria has been described in which the diagnosis was confirmed by the demonstration of uroporphyrin in the urine and by spectroscopic examination.

The clinical picture in this case was characterized by attacks of voiding dark red urine (port wine color) and various types of gastrointestinal disturbances, jaundice, menstrual disturbances and mild mental depressions.

The treatment consisted of plasma and whole blood transfusions and large doses of vitamin B and vitamin C, all of which seemed to have but temporary effect on the condition.

This case is of special interest because the failure to recognize this condition in the incipient stage led to several false diagnoses with subsequent unnecessary surgical operations, all of which failed to control, improve or cure the condition.

BIBLIOGRAPHY

1. DUNCAN, G. G.: Diseases of metabolism. 1943, W. B. Saunders Company, Philadelphia.
2. ELDAHL, A.: Case of acute porphyria developed during hospitalization, *Acta med. Scandinav.*, 1938, xcvi, 415-419.
3. FETTER, F., HUMPHREY, A. A., and LONGENECKER, CH. R.: Acute idiopathic porphyria, *U. S. Naval Med. Bull.*, 1944, xliii, 349-352.
4. GARROD, A. E.: Inborn errors of metabolism, 1923, H. Froude, Hodder and Stoughton, London.
5. GEISSLER, J.: Zur Kenntnis der Porphyria acuta, *Klin. Wchnschr.*, 1939, xviii, 378-380.
6. GUNTHER, H.: Die Hematoporphyrie, *Deutsch. Arch. f. klin. Med.*, 1911, cv, 89-146.
7. KUHNAU, W. W.: Experimentelle Untersuchungen ueber die Beziehungen des Nikotinsaeureamids zum Porphyrinstoffwechsel und zur Lichtwirkung, *Strahlentherapie*, 1939, lxvi, 24-39.
8. MASON, V. R., COURVILLE, C., and ZISKIND, E.: Porphyrins in human disease, *Medicine*, 1933, xii, 355-439.
9. NESBITT, S., and WATKINS, CH. H.: Acute porphyria, *Am. Jr. Med. Sci.*, 1942, cciii, 74-83.
10. ROSENBLUM, L. A., and JOLLIFFE, N.: Porphyrinuria in pellagra, *Am. Jr. Med. Sci.*, 1940, cii, 853-858.
11. WATSON, C. J.: The porphyrins and their relation to disease: Porphyria, in Christian and MacKenzie's *Oxford Medicine*, 1938, iv, 1-34, Oxford University Press, New York.

HODGKIN'S DISEASE INVOLVING THE PITUITARY GLAND WITH DIABETES INSIPIDUS *

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HODGKIN's granuloma is a fairly common entity, but involvement of the pituitary gland with symptoms is rarely encountered. In a survey of the literature, only four cases of lymphogranuloma of the hypophysis were found, one case

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without symptoms and the other three showing the symptoms of diabetes insipidus. A case of the later type is described.

CASE REPORT

The patient, M. C. S., was a white male, aged 47, a farmer, admitted March 24, 1945. The family history and the past history presented nothing of significance. The patient had been in good health until August 1944 when he first noticed the appearance

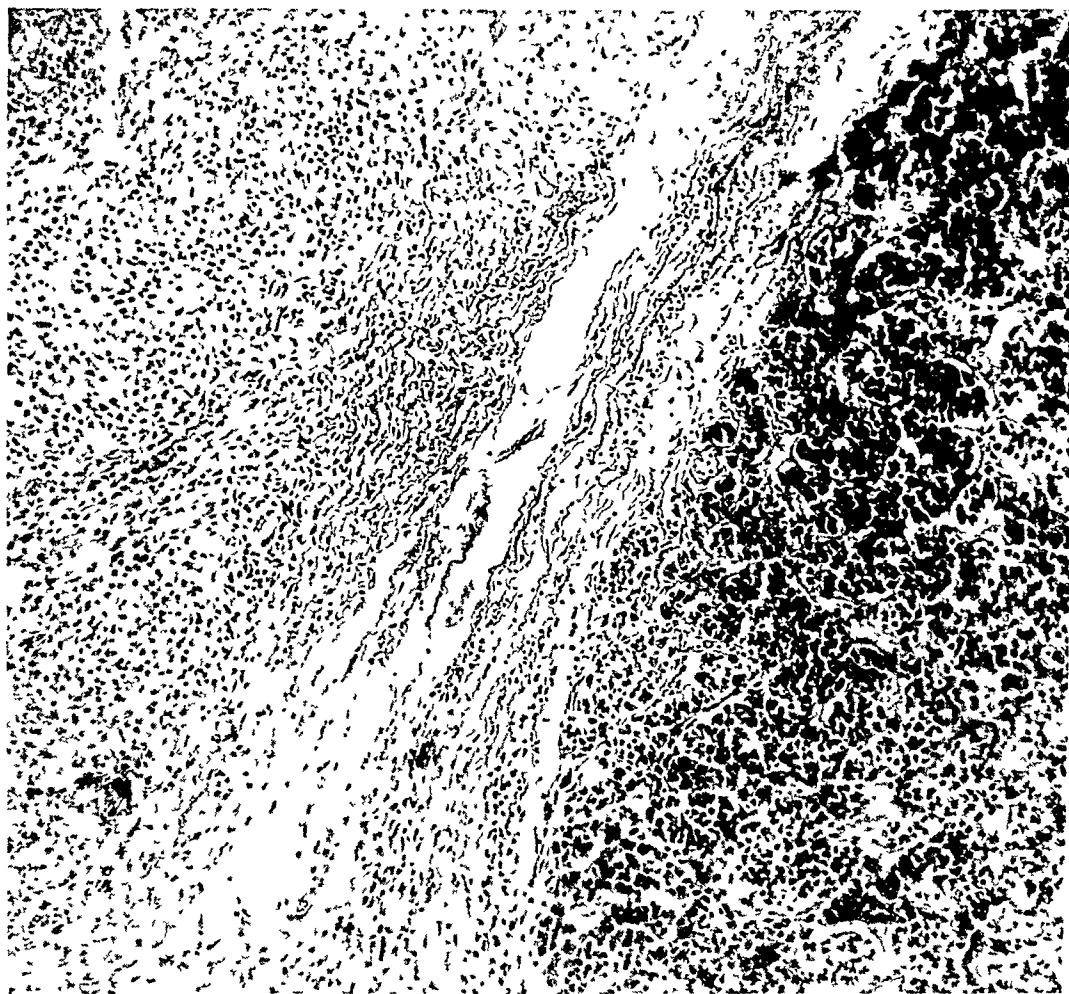


FIG. 1. Low power photomicrograph of a section through the anterior and posterior lobes of the hypophysis, showing round cell infiltration and multinucleated giant cells along with an increase in fibrous stroma. $\times 100$.

of "lumps" on the left side of the neck. These gradually increased in size but caused him no particular discomfort. Later, he noticed smaller masses on the right side of his neck, axilla and groin. He stated that he had lost a great deal of weight.

Since February 1945, the patient had developed a progressively increasing weakness and a severe thirst. He stated that he drank about three gallons of water daily and urinated an almost equal quantity. He did not notice any polyphagia associated with the polydipsia and polyuria.

Physical examination disclosed bilateral enlargement of lymph nodes in the neck, axillary and inguinal regions. The nodes varied in size from 1 cm. to 3 cm. in diameter. They were firm and some appeared to be coalesced, but most of them were discrete. Palpation of the nodes showed mild tenderness on pressure. The skin was dry and loose. The patient had a temperature of 103° F. on admission.

Radiographs of the chest revealed pulmonary emphysema. No mediastinal enlargement was seen. Radiographs of the skull revealed a normal sella turcica and normal anterior and posterior clinoid processes.

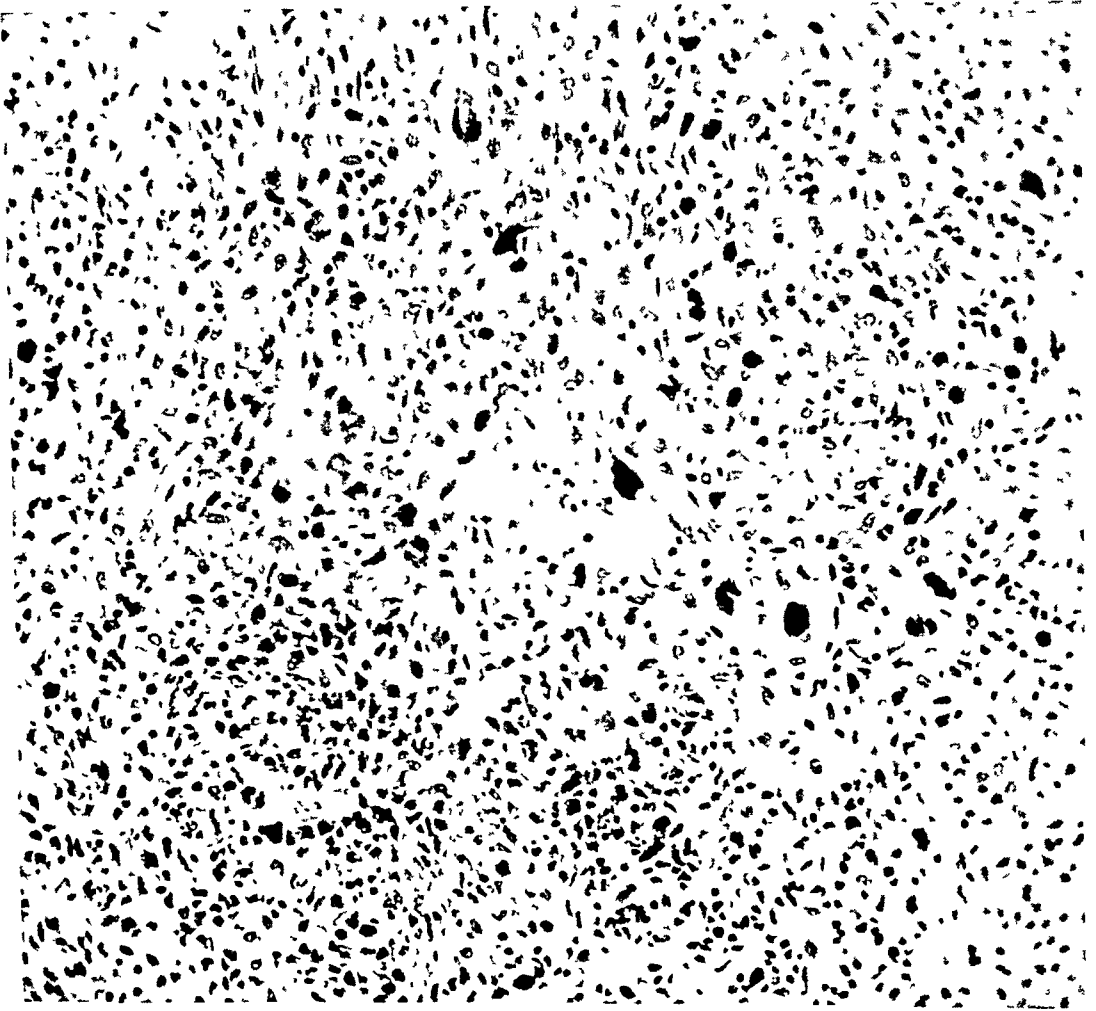


FIG. 2. Higher power photomicrograph of a section through the posterior lobe of the pituitary gland, showing the typical multinucleated Dorothy Reed giant cells of Hodgkin's disease. $\times 200$

The percentage of hemoglobin and the red and white blood cell counts were normal. Wassermann reaction was negative. The urinalysis was negative except for a low specific gravity, readings varying from 1.004 to 1.008. The urinary output for 24 hour periods varied from 3000 c.c. to 7900 c.c. A urine concentration test revealed poor concentrating power. The blood sugar was 74.1 mg. per 100 c.c. Glucose tolerance tests were normal, the urine on all occasions being negative for sugar.

The temperature was of a relapsing type characterized by elevations reaching 103° F. separated by periods of normal temperature.

Biopsy of a cervical lymph node established the diagnosis of Hodgkin's disease.

For the treatment of Hodgkin's disease, the patient received 12 doses of deep roentgen therapy. Each treatment consisted of 150 r for 6.75 minutes applied alternately to the right groin and left neck. However, the patient showed no favorable response. For the diabetes insipidus, pitressin tannate was given intramuscularly and the polydipsia and polyuria subsided slightly. Before the full effect of this treatment could be determined, the patient developed intestinal obstruction and died.

Autopsy disclosed enlarged lymph nodes in the cervical, axillary and inguinal regions. Some were discrete and others were fused. Section of the nodes revealed a pale gray, homogeneous surface. Examination of the abdominal cavity disclosed an intussusception of the small intestine at the junction of the lower and middle thirds. The intussusception was three inches in length and the exciting cause of the process was a Hodgkin's node. Proximal to this, an area of bowel six inches long was found to be completely necrotic. The remaining small bowel proximal to the necrotic area was markedly dilated and congested. The spleen was enlarged and firm and showed increased fibrosis throughout. The gall-bladder contained a stone about the size of a walnut.

Examination of the cranial cavity disclosed the pituitary gland to be enlarged to about 1.5 cm. in diameter. On section, it was pale gray in color. Both lobes could be differentiated. The sella turcica was intact and no destruction was seen. The surrounding dura mater was not involved.

Histologic examination of a lymph node from the inguinal region disclosed a marked increase in fibrous stroma throughout the section. The lymph follicles were distorted and partly destroyed. Many large mononuclear cells were present with an increase in lymphocytes and eosinophile cells. The spleen disclosed an increase in fibrosis and reticulum cell hyperplasia. The pituitary gland showed infiltration of the anterior and posterior lobes. Both lobes showed a moderate amount of fibrosis. Many large mononuclear cells and some plasma cells were seen. Occasional eosinophile cells were encountered. Many typical multinucleated Dorothy Reed giant cells were also present. The histological picture was characteristic of Hodgkin's disease. Infiltration was more marked in the posterior lobe. A moderate number of neuroglial cells remained in the posterior lobe. The anterior lobe showed one small area of necrosis and many unaltered areas of chromophile and chromophobe epithelial cells.

DISCUSSION

Searching the literature, we encountered only four cases of lymphogranuloma in the pituitary gland. Of these, one did not show symptoms of diabetes insipidus. Three cases in which the diabetes insipidus syndrome developed also showed various neurological symptoms due to involvement of nerve tissue by the lymphogranuloma.

Falta and Spitzenberger (1937) in Germany, reported the case of a woman, aged 42, who was admitted with painful infra- and supraclavicular glands and difficulty in swallowing. Roentgenograms showed mediastinal enlargement. A tentative diagnosis of lymphogranuloma was made. The patient received a course of roentgen therapy and improved. Later, pain developed in the shoulders and arms along with a facial neuralgia, an enlargement of the axillary and inguinal glands, and herpes zoster. Still later, polydipsia and polyuria occurred. Pneumonia developed and death ensued. Autopsy revealed involvement of the mediastinal and mesenteric lymph nodes, the kidneys, the fourth and fifth lumbar vertebrae, the nasopharynx and the pituitary gland with typical lymphogranulomatous tissue.

Desbuquois (1935) in France reported a case of a man, aged 32, who was admitted with cervical adenitis, loss of weight, asthenia and intermittent fever. Roentgenograms showed enlargement of mediastinal lymph nodes. The enlarged nodes were painful, hard, indurated, coalescent and adherent to the deeper structures. Biopsy revealed a lymphogranuloma. Roentgen therapy was instituted and the adenopathy regressed. Polydipsia and polyuria occurred along with symptoms of a cerebral encephalopathy. Roentgen irradiation of the cranium resulted in disappearance of the headaches and a decrease in polyuria. Finally, symptoms of diabetes mellitus, glycosuria and hyperglycemia, occurred. A short time later the patient died. This case presents diabetes mellitus and diabetes insipidus in the same patient, the latter due to the lymphogranuloma.

Flose (1941) in Brazil reported the third case in medical literature. This was an adult with progressive swelling of the right inguinal lymph nodes and three years later, swelling of the left inguinal nodes. Later, there occurred a generalized lymph node hyperplasia and splenic enlargement. Following this, motor and sensory disturbances became apparent, and the lesions were localized to the second, third, seventh, ninth, tenth and twelfth cranial nerves on the left. Roentgenograms showed involvement of the lesser and greater wings of the sphenoid bone. Biopsy of the lymph node revealed a malignant lymphogranuloma. The patient received roentgen therapy and improved temporarily. The motor disturbances disappeared as did the splenic enlargement. Later, the disease became aggravated by a typical diabetes insipidus syndrome due to the localization of the lymphogranuloma in the hypophysis.

Törne (1941) in Germany found a lymphogranuloma of the pituitary gland as an incidental finding in a systematic study of many pituitary glands. Clinical symptoms were missing. The man, aged 73, was admitted for cervical lymph node enlargement and given the diagnosis of generalized lymphogranulomatosis. The patient died of pneumonia and at autopsy was found to have lymphogranulomatosis of the cervical, mental, axillary, mediastinal, mesenteric, preaortic and paragastric lymph nodes. Typical foci were also seen in the spleen, liver, left kidney, pericardium, dura mater, and the pituitary gland. Histology of the lesions disclosed many multinucleated giant cells, many eosinophile leukocytes and fibrous tissue in greater abundance than cellular tissue.

The case reported in this paper shows the similarity in symptoms resulting from a lymphogranuloma involving the pituitary gland. The whole pituitary gland was infiltrated. The posterior lobe was almost completely destroyed whereas the anterior lobe was only moderately involved. This condition is necessary in order for diabetes insipidus to result; that is, the posterior lobe must be destroyed while the anterior lobe must be intact or at least sufficiently functioning. The explanation for this is based on a hormonal control. It has been established that the anterior lobe contains a diuretic hormone and the posterior lobe an anti-diuretic hormone which normally balance one another.

In this case, the neural or posterior lobe involvement caused a diminution or total absence of the anti-diuretic hormone. On the other hand, the pars anterior was involved to a lesser degree and still functioned sufficiently to allow the diuretic factor to act unchecked. Thus we see the reason for the polyuria. Total extirpation of the pituitary gland does not result in diabetes insipidus

because the diuretic factor of the pars anterior is removed along with the anti-diuretic principle of the neural division.

Diabetes insipidus may also result when the lesion is situated anywhere along the hypothalamico-hypophyseal tract. This tract is composed of nerve fibers which run from the hypothalamus to the pars nervosa or posterior lobe. The nerve fibers arise chiefly in the supraoptic nucleus of the hypothalamus and course through the median eminence and infundibulum stem into the pars nervosa and is known more specifically as the supraoptico-hypophyseal tract. A lesion in this tract will cause degeneration of the tract, atrophy of the supraoptic nucleus and atrophy of the neural lobe of the hypophysis.

The present concept of the physiology of diabetes insipidus is well presented in the papers of Fisher, Ingram and Ranson.³ They support the view that diabetes insipidus is essentially a hormonal disturbance, although the secretion of the anti-diuretic hormone is under the nervous control of the hypothalamus.

The supraoptico-hypophyseal system regulates the secretion of the anti-diuretic hormone by the neural division of the hypophysis. An interruption of this system by a section or lesion may occur at three sites. It may occur in the hypothalamus and cause the neural division (pars nervosa, median eminence, and infundibulum stem) to become atrophic and functionally inactive, thus leading to a deficiency of the anti-diuretic hormone. Likewise, it may occur in the infundibulum stem high enough to cut all of it and the median eminence away from the hypothalamus and bring about a similar atrophy and deficiency. Finally, extirpation or invasion with destruction of the neural division in all its parts leads to the same hormonal deficiency by virtue of the fact that it removes the site of formation of the anti-diuretic principle. This leads to polyuria followed by a secondary and compensatory polydipsia. The polyuria represents the result of diuretic processes in the body unchecked by the anti-diuretic mechanism. These diuretic processes are normally under the control of the pars anterior of the hypophysis. Normally, there is a balance between the diuretic action of the anterior lobe and the anti-diuretic effect of the posterior lobe.

Thus, diabetes insipidus is essentially an hypophyseal deficiency syndrome caused by a diminution or total absence of the anti-diuretic hormone of the neural lobe of the hypophysis. This occurs when the latter is extirpated, destroyed or becomes atrophic secondary to interruption of the supraoptico-hypophyseal tracts, either by a section or a lesion.

SUMMARY

A case of Hodgkin's disease involving the pituitary gland with resulting diabetes insipidus, proved by autopsy, is reported. This is the fourth case in medical literature.

BIBLIOGRAPHY

1. DESBUQUOIS, M. G.: Sur un cas de lymphogranulomatose maligne compliqué de diabète insipide, *Bull. e. mém. Soc. méd. d. hôp. d. Paris*, 1935, li, 1355-1362.
2. FALTA, W., and SPITZENBERGER, O.: Ein Fall von Diabetes insipidus durch Lymphogranulom de Dingt, *Strahlentherapie*, 1937, ix, 385-392.
3. FISHER, C., INGRAM, W. T., and RANSON, S. W.: Diabetes insipidus and the neuro-hormonal control of water balance, 1938, Edwards Brothers, Inc., Ann Arbor, Michigan.

4. FLOSI, A. Z.: Sobre um caso de diabetes insipidus condicionado á linfogranulomatose maligna, *Arq. de cir. clin. e exper.*, 1941, 1027-1054.
5. RANSON, S. W., FISHER, C., and INGRAM, W. K.: Hypothalamico-hypophyseal mechanism in diabetes insipidus, *Am. Res. Nerv. and Ment. Dis., Proc.*, 1936, xvii, 410.
6. TÖRNE, H. V.: Lymphogranulomatose der Hypophyse, *Zentralbl. f. allg. Path. u. path. Anat.*, 1941, lxxvii, 305-307.

MAGNESIUM SULFATE IN PAROXYSMAL TACHYCARDIA *

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It has long been known that the magnesium ions act as a depressant to cardiac musculature. Smith, Winkler, and Hoff¹ reported bradycardia, conduction disturbances and eventually cardiac arrest with high concentration resulting from parenteral administration. However, it was not until Boyd and Scherf² reported their series of cases that the therapeutic effect and beneficial results of magnesium salts in paroxysmal tachycardia were generally recognized. The effect of intravenous injections of magnesium sulfate in 10 cases of paroxysmal tachycardia and one case of flutter was studied. They found that the injection of a 10 per cent solution was beneficial in three out of eight attacks, whereas a 20 per cent solution was beneficial in eight out of eight attacks. Consequently, the use of a 20 per cent solution was advocated. Disturbances of conduction and ventricular extrasystoles appeared for a short time after the injection. These investigators used 10 to 20 cubic centimeters of the solution for each injection. They recommended that the initial treatment of any attack of paroxysmal tachycardia consist of a trial of the various vagal reflexes. Medicinal therapy is justified only when these reflexes prove useless. Because intravenous quinidine or the use of mecholyl is not always innocuous, they believe that the intravenous use of magnesium sulfate merits a definite place among these drugs in the medicinal management of these disorders. No untoward effects were encountered in their series. Because of the paucity of cases we would like to present another case treated successfully with magnesium sulfate. Also, the dosage of magnesium sulfate used was relatively large according to Boyd and Scherf's recommendations.

CASE REPORT

A. V., 57, white, Italian male, was admitted to the Rhode Island Hospital May 3, 1945. A few hours before admission he was found lying in bed unable to move his right arm or leg. Previous history was negative.

Physical examination showed a well nourished and well developed male who appeared very drowsy. He answered questions with a marked slurring of speech. Blood pressure was 180 mm. Hg systolic and 110 mm. diastolic. There was marked right sided facial weakness and loss of motor power of the right arm and leg. Reflexes were hyperactive on the right side with a positive Babinski and Chaddock on that side. The spinal fluid showed an increase in pressure and uniformly bloody fluid

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in three tubes. The pulse on admission was 88 and his respirations were 22. The diagnosis of subarachnoid hemorrhage and right hemiplegia was made at this time.

Course in hospital: On the third hospital day the patient's pulse suddenly rose to above 200. The apical sounds were very rapid and regular. Radial pulse was felt with difficulty. Carotid sinus pressure and ocular pressure did not alter the pulse rate.

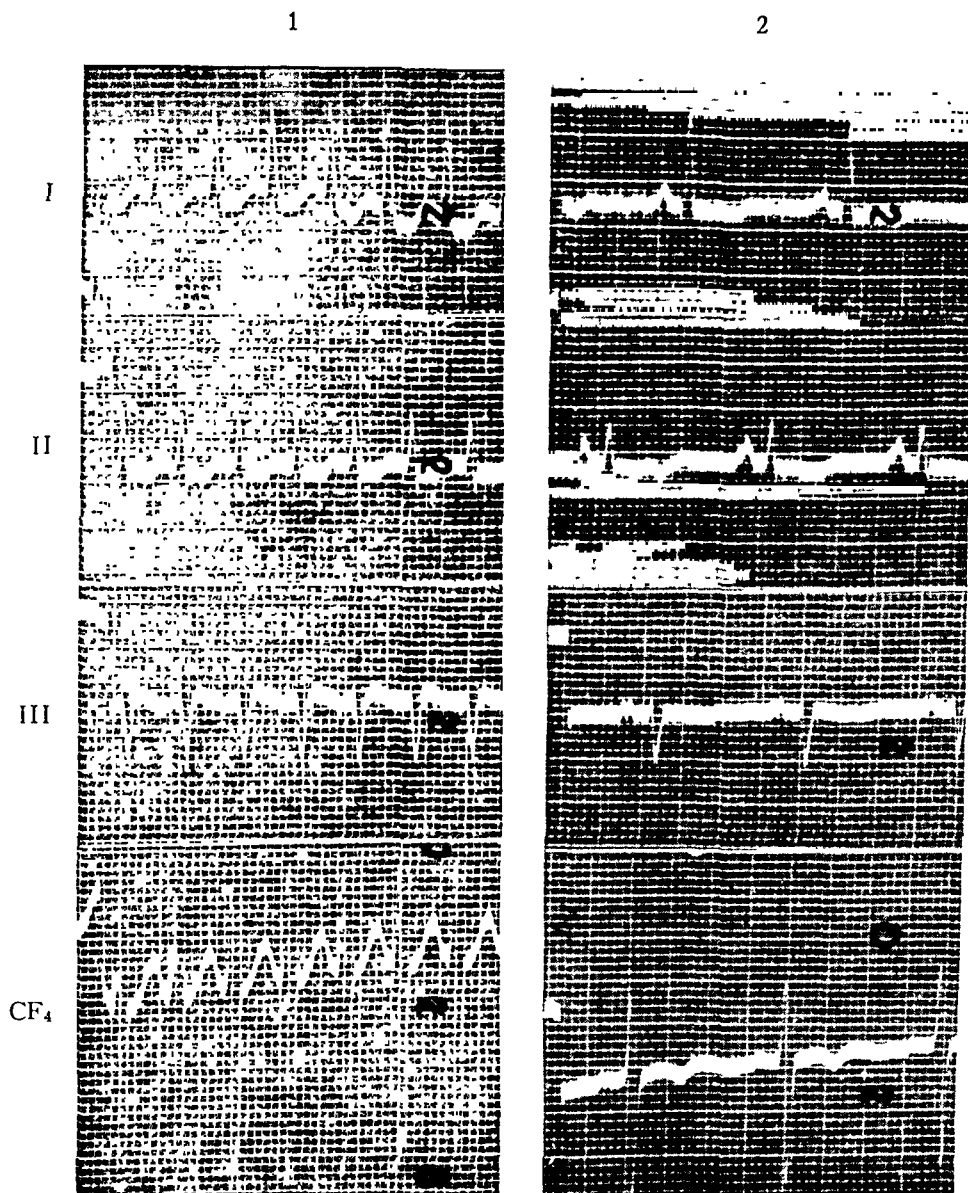


FIG. 1. 1. Before administration of magnesium sulfate. 2. After administration of magnesium sulfate.

An electrocardiogram taken at this time showed a paroxysmal auricular tachycardia with a rate of 240 per minute. Quinidine sulfate, three grains, was started intramuscularly every two hours. He received a total of 18 grains in 12 hours with no effect. Lanatocid-C (Cedilanid), 0.8 mg., was given intravenously and the patient continued on 0.1 gm. of digitalis leaf every four hours. This rapid digitalization also

had no effect. Because of the patient's poor condition it was thought advisable to try to stop the arrhythmia if possible.

Mecholyl was then tried. Twenty-five mg. were given subcutaneously with no effect. Four hours later 10 c.c. of 25 per cent magnesium sulfate were given intravenously with no effect. The patient's temperature had risen to 104° F. by rectum. Six hours later he was given 22 c.c. of 25 per cent magnesium sulfate intravenously. While the needle was still in his vein, his apical beat suddenly slowed to 88 per minute. An electrocardiogram obtained at this time showed regular sinus rhythm with a rate of 76 per minute. The paroxysm had lasted 28 hours. The patient gradually improved and he was continued on digitalis, 0.1 gm. daily.

SUMMARY

1. The effect of intravenous magnesium sulfate on a case of paroxysmal tachycardia is presented.

2. The patient received 10 c.c. of 25 per cent solution with no effect. Six hours later he received 22 c.c. of a 25 per cent solution with immediate cessation of the tachycardia.

BIBLIOGRAPHY

1. SMITH, P. K., WINKLER, A. W., and HOFF, H. F.: Electrocardiographic changes and concentration of magnesium serum following intravenous injection of magnesium salts, *Am. Jr. Physiol.*, 1939, cxxvi, 720-730.
2. BOYD, L. J., and SCHERF, D.: Magnesium sulfate in paroxysmal tachycardia, *Am. Jr. Med. Sci.*, 1943, ccvi, 43.

EDITORIAL

FOLIC ACID

ANEMIA developing as a result of a diet deficient in vitamins has been described in a number of species of animals. One of the earliest observations was that of Wills and Bilimoria¹ (1932). Monkeys fed a deficient diet similar to that customarily consumed by the poorer classes in India developed a macrocytic anemia, accompanied by leukopenia, granulocytopenia, and a megaloblastic hyperplasia of the bone marrow, which could be relieved by feeding marmite (yeast extract). This anemia closely resembled that seen in human cases of nutritional macrocytic anemia. This work has been confirmed and extended by subsequent observers, notably by Day and associates.² Monkeys on a deficient diet developed a progressive fatal disease characterized by anemia, leukopenia, ulceration of the gums and often diarrhea. This could be prevented by feeding adequate amounts of brewers' yeast or liver extract. To the active substance they applied the term "vitamin M."³ They together with others later showed that this effect was not produced by any of the recognized members of the vitamin B complex, including thiamin, riboflavin, niacin, calcium pantothenate, pyridoxin hydrochloride, sodium para-amino-benzoate, choline, or inositol.

In 1939 Hogan and Parrott⁴ showed that chicks on a special diet adequate in all the essential factors then recognized failed to grow, and developed a macrocytic hyperchromic anemia. This could be prevented or relieved by a water-soluble liver extract. They designated the active substance as vitamin B_c. Similar anemias have been produced in rats and in pigs.

The study of the substance which prevents the development of anemia in these animals has been facilitated and promoted by observations on the growth requirements of certain bacteria. In 1940 Snell and Peterson⁵ reported that on a basal medium consisting of hydrolyzed casein, tryptophane and several of the then known members of the vitamin B₂ complex, no growth of *Lactobacillus casei* would occur unless extracts of certain plant or animal tissues were added to the medium. Yeast and liver contained this growth factor (*L. casei* factor) in relative abundance. By adsorption on norite and subsequent elution they were able to remove the active ma-

¹ WILLS, L., and BILIMORIA, H. S.: Studies in pernicious anemia of pregnancy: production of macrocytic anemia in monkeys by deficient feeding, Indian Jr. Med. Res., 1932, xx, 391.

² DAY, P. L., LANGSTON, W. C., and SHUKERS, C. F.: Leukopenia and anemia in the monkey resulting from vitamin deficiency, Jr. Nutr., 1935, ix, 637.

³ DAY, P. L., LANGSTON, W. C., and DARBY, W. J.: Failure of nicotinic acid to prevent nutritional cytopenia in the monkey, Proc. Soc. Exper. Biol. and Med., 1938, xxxviii, 360.

⁴ HOGAN, A. G., and PARROTT, E. M.: Anemia in chicks caused by a vitamin deficiency, Jr. Biol. Chem., 1940, cxxxii, 507.

⁵ SNELL, E. E., and PETERSON, W. H.: Growth factors for bacteria. X. Additional factors required by certain lactic acid bacteria, Jr. Bact., 1940, xxxix, 273.

terial from these extracts and obtain it in a state of relative purity and high concentration.

In 1941 Mitchell, Snell and Williams⁶ obtained from spinach a similar factor which stimulated the growth of *Streptococcus lactis* R (*S. lactis* factor), for which they suggested the name "folic acid" because of the source of the material. This also stimulated the growth of *L. casei* with about the same degree of potency. They devised a method of microbiological assay of these factors which depends in principle upon the determination by titration of the minimal amount of material which stimulates growth of these organisms in the basal medium.

The relationship of the *L. casei* factor to the *S. lactis* factor, and the part they play in the nutrition of animals have been the subject of many investigations which are far too numerous to review here. The subject is complicated, and the identity or exact relationship of the factors obtained by different investigators has not yet been definitely determined. For details the reader is referred to the recent excellent summary of Berry and Spies.⁷

Although the "folic acid" of Snell et al. promoted the growth of these two organisms to about the same degree, other materials were found which stimulated the growth of *S. lactis* but had little or no effect on *L. casei*. If, however, *S. lactis* is allowed to grow in a medium containing such material the supernatant fluid from the culture may be potent in stimulating growth of *L. casei*. With certain other materials the reverse relationship has been observed. An alteration of the factor produced by the growth of one species may be necessary to make it available for the other.

Other materials which have little or no growth-promoting activity for these bacteria (but which may be utilizable by the chick) may become potent if first subjected to the action of an enzyme isolated from certain organs, such as the liver, kidney, pancreas or spleen of the rat or other species of animals. This has led to the hypothesis that the potentially active growth factor occurs in certain extracts in inactive form as a conjugate with other (non-protein) materials. Different organisms apparently vary in their capacity to utilize such material, depending conceivably on their capacity to produce an enzyme which will split the compound and liberate the "active" fraction.

The quantity of active material required to promote growth is very minute, as little as 0.00012 γ of Mitchell's "folic acid" per ml. of medium sufficing to produce half maximal growth of *L. casei*.⁶

The chemical structure of at least one of these growth factors has been determined. Angier et al.⁸ have synthesized a compound which appears to be identical in its physiological action (in chicks) and in its important

⁶ MITCHELL, H. K., SNELL, E. E., and WILLIAMS, R. J.: The concentration of "folic acid," Jr. Am. Chem. Soc., 1941, lxiii, 2284.

⁷ BERRY, L. J., and SPIES, T. D.: The present status of folic acid, Blood, 1946, i, 271.

⁸ ANGIER, R. B., et al.: The structure and synthesis of the liver *L. casei* factor, Science, 1946, ciii, 667.

physical and chemical properties with the crystalline *L. casei* factor (folic acid) isolated from liver.

The immediate practical importance of these bacterial growth factors arises from the fact that they are also essential for normal nutrition in animals. It has been shown by numerous investigators that folic acid concentrates will maintain normal growth and prevent or relieve (in large measure, at least) the granulocytopenia, macrocytic anemia and thrombocytopenia that develop in monkeys^{9,10} and chicks¹¹ kept on the type of deficient diet already described. Folic acid appears to be identical in its physiological action with vitamin M in monkeys and with vitamin B₁₂ in chicks.

In the case of man, early observations, particularly of Wills and other British investigators, showed that certain nutritional macrocytic anemias, including "pernicious anemia" of pregnancy, responded well to marmite and to crude liver preparations (which contain folic acid). In some cases the response was much better to these than to highly purified liver extracts containing Castle's erythrocyte maturing factor.

The effectiveness of *L. casei* factor in curing nutritional macrocytic anemia in monkeys led naturally to a trial in similar anemias in man. Passing by several earlier and less conclusive reports, Vilter, Spies and Koch¹² in 1945 reported the treatment of 14 cases of macrocytic anemia with *L. casei* factor, using the synthetic folic acid. These included six cases of nutritional anemia, five cases of pernicious anemia, and three cases of undetermined nature. The drug was administered both orally and parenterally, usually in an oral dose of 50 mg. twice a day, or parenterally, 20 mg. a day. In all but one case (classed as nutritional anemia) highly satisfactory results were obtained. A reticulocytosis ranging from 6 to 21 per cent appeared, reaching the peak on the fourth to the tenth day. This was accompanied and followed by a progressive rise in red blood cells and hemoglobin, which reached normal in cases in which treatment was continued. In most of those cases with a leukopenia, the leukocytes also rose to normal figures. There was corresponding improvement in clinical symptoms, usually evident subjectively on the third to the fifth day. The patients felt better and stronger, there was a return of appetite and a gain in weight. In some cases there was a cessation of diarrhea when present, and relief from burning of the tongue and oral mucous membranes. Spies¹³ has subsequently summarized the results obtained in 27 cases of macrocytic anemia (including the 14 previously mentioned), which were equally favorable,

⁹ WILSON, H. E., et al.: Reactions of monkeys to experimental respiratory infections. V. Haematological observations in nutritional deficiency states, Proc. Soc. Exper. Biol. and Med., 1942, 1, 341.

¹⁰ WAISMAN, H. A., and ELVEHJEM, C. A.: The role of biotin and "folic acid" in nutrition of the Rhesus monkey, Jr. Nutr., 1943, xxvi, 361.

¹¹ HUTCHINGS, B. L., et al.: Relation of a growth factor required by *Lactobacillus casei* to the nutrition of the chick, Jr. Biol. Chem., 1941, cxi, 681.

¹² VILTER, C. F., SPIES, T. D., and KOCH, M. B.: Further studies on folic acid in the treatment of macrocytic anemias, South. Med. Jr., 1945, xxxviii, 781.

¹³ SPIES, T. D.: Effect of folic acid on persons with macrocytic anemia in relapse, Jr. Am. Med. Assoc., 1946, cxxx, 474.

and regarded as comparable with those obtained with liver extract. Available data are insufficient to determine whether folic acid is equally effective, and there is now no reason to believe that it will prove superior to liver extract. In two patients with pernicious anemia who had become sensitized to liver extract, folic acid was substituted "safely and satisfactorily."

Folic acid was without effect in three cases of aplastic anemia, four cases of iron deficiency anemia and three cases of anemia due to leukemia.

In these cases, the response to oral administration was regarded as somewhat better than to parenteral injections, but the oral dose was five times as large. Spies states that marked responses have been obtained in some cases with as little as 10 mg. per day by mouth and 5 to 10 mg. parenterally. The minimal effective dose and the optimal dose have not been determined, but 400 mg. per day has been given orally without bad effects. It does not affect the blood of normal individuals.

Confirmatory reports by other observers have recently appeared. Moore et al.¹⁴ reported successful treatment of four cases, including two cases of pernicious anemia. Doan et al.¹⁵ report obtaining satisfactory clinical results with synthetic *L. casei* factor in selected cases, and report one case of pernicious anemia which gave a maximal response to 2 mg. per day intravenously over a period of 20 days. (Spies, however, has observed cases in whom 3 to 4 mg. a day did not cause a satisfactory response.) In three cases hypersensitive to liver extract, folic acid was substituted with satisfactory results.

Amill and Wright¹⁶ also have reported the successful treatment of six unselected cases of pernicious anemia with synthetic *L. casei* factor.

Highly satisfactory results have also been obtained in treatment of sprue. Darby et al.¹⁷ reported the successful treatment of three cases with synthetic *L. casei* factor. Spies and associates¹⁸ reported the successful treatment of nine cases of tropical sprue in Cuba. A more complete report of this work was presented at the meeting of the American College of Physicians (May, 1946) and will be published in an early number of the *Annals of Internal Medicine*.

The hematopoietic response in these cases was quite like that in the other types of macrocytic anemia. There was a reticulocytosis ranging from 12.5 to 32 per cent, which was a maximal response according to the

¹⁴ MOORE, C. V., BIERBAUM, O. S., WELCH, A. D., and WRIGHT, L. D.: The activity of synthetic *Lactobacillus casei* factor ("folic acid") as an anti-pernicious anemia substance. I. Observations on four patients: Two with Addisonian pernicious anemia, one with non-tropical sprue and one with pernicious anemia of pregnancy, Jr. Lab. and Clin. Med., 1946, xxx, 1056.

¹⁵ DOAN, C. A., WILSON, H. E., and WRIGHT, C. S.: Folic acid (*L. casei* factor), an essential pan-hematopoietic factor: experimental and clinical studies, Ohio State Med. Jr., 1946, xlii, 139.

¹⁶ AMILL, L. A., and WRIGHT, M.: Synthetic folic acid therapy in pernicious anemia, Jr. Am. Med. Assoc., 1946, cxxxi, 1201.

¹⁷ DARBY, W. J., JONES, E., and JOHNSON, H. C.: The use of synthetic *L. casei* factor in the treatment of sprue, Science, 1946, ciii, 108.

¹⁸ SPIES, T. D., et. al.: Observations on the treatment of tropical sprue with folic acid, Jr. Lab. and Clin. Med., 1946, xxxi, 227.

standard of Minot and Castle for liver extract in pernicious anemia. There was a progressive rise in hemoglobin and in red blood cells, ranging from 0.46 to 1.2 million in 14 days. In three cases examined the marrow reverted to a normoblastic type of hyperplasia. There was a corresponding improvement in subjective symptoms, with increased appetite, gain in weight and strength and increase in vigor and alertness. The burning and objective evidences of glossitis subsided. In most cases the diarrhea largely or entirely subsided, and the feces tended to return to normal in bulk and gross appearance. Usually, however, the stools did not become completely and permanently normal. The period of observation, however, has been relatively short, and the (experimental) diet not optimal and probably deficient in some other respects.

Three patients who were given 10 mg. a day responded about as well as those who received 100 mg.

The mechanism of the action of folic acid and its relation to other known hematopoietic factors have not been demonstrated. Since it is active on parenteral injection, folic acid can not be the intrinsic factor of Castle. For the same reason and because it does not depend upon the action of gastric juice for its activity it is probably not identical with extrinsic factor, although it is still possible folic acid may be related in some way to the latter. It is probably not the active material (E. M. F.) in liver, since the required dose of folic acid is many times larger than the amount contained in an effective dose of potent liver extract. To go farther than this is to indulge in what is largely speculation. Spies,⁷ however, has advanced the interesting suggestion that folic acid may be ingested and possibly stored in the tissues in the form of an inactive conjugate. In pernicious anemia there may be a lack of enzymes which can split off the folic acid. Potent liver extract may act by liberating the active fraction in utilizable form. It seems likely that folic acid in some way functions as part of an essential enzyme system, and that its rôle is not limited to its hematopoietic functions.

The part that folic acid will take in practical therapeutics is still uncertain, particularly the extent to which it may supplant the use of liver extracts. It is not yet certain that folic acid is fully equal to liver extract in maintaining remissions, and particularly in preventing the development of neurological degenerations in pernicious anemia. It seems improbable that it will be any more effective. Apparently folic acid is a satisfactory substitute, at least for a short period, in patients who are hypersensitive to liver extracts. If it proves to be as effective as liver extract, it will have an important advantage from the pharmaceutical standpoint in eliminating the difficulty—which is getting increasingly urgent and acute—of finding enough untreated cases of pernicious anemia on whom to test the potency of commercial liver extracts.

REVIEWS

The Physiological Basis of Medical Practice. By CHARLES HERBERT BEST, C.B.E., M.A., D.Sc. and NORMAN BURKE TAYLOR, V.D., M.D., F.R.S. Fourth Edition. 1169 pages; 26.5 × 17 cm. 1945. Williams & Wilkins Co., Baltimore. Price, \$10.00.

The continued success of "The Physiological Basis of Medical Practice" is shown in the demand which has necessitated thirteen printings and four editions in eleven years. The format of this edition has been changed. Double columns and larger pages make it easier both to read and to handle. The moderated reduction in the size of many of the diagrams and illustrations, together with the deletion of outmoded material has made room for much new material without a marked increase in the size of the volume.

The chapter on intracellular oxidations by Dr. Wyne has been markedly improved by rewriting. Much more material is included than in the previous editions and it is presented in a more systematic fashion. A number of type reactions are shown which demonstrate oxidative systems and a new diagram (from Potter 1944) shows the inter-relationships between the phosphorylating, glycolytic and respiratory systems.

The references are grouped by chapters at the end of the book. They are divided into two sections: specific references to original articles and monographs and reviews. The material is carefully cross indexed. The few errors found in no way detract from the value of the volume.

M. A. A.

About Ourselves. By JAMES G. NEEDHAM, Ph.D. 276 pages; 26 × 18 cm. 1941. Jaques Cattell Press, Lancaster, Pa. Price, \$3.00.

This book might be considered an introduction to the study of sociology, written from the viewpoint of a zoölogist. The author presents, in a simple, non-technical form, the contributions of zoölogy to the knowledge of the human species, together with his thinking as to the relation of this knowledge to the organization of society. The book is divided into two parts: Part I, "Man in His Biological Aspects", is an excellent summary of man's evolution and place in the animal world, the similarities and difference between us and other animals, the development of human behavior, and the nature of instincts. Part II, "Society in Its Biological Aspects," discusses the distinction between man's social and biological inheritance, traces the development of socially determined behavior (always relating this to the instinctive needs out of which it arose) and ends with some chapters on war, government and religion in their biological aspects.

Part I and sections of Part II are written with a simplicity and clarity which obviously arise from the author's thorough familiarity with his subject. Particularly valuable is the exposition of instinctive behavior which includes a thoughtful discussion of the characteristics of instincts, profusely illustrated with recollections and anecdotes of the barnyard, zoo, jungle, nursery, and battlefield. One feels that Dr. Needham's thoughts on instinctive behavior are written by one who has watched it with joy and fascination for a long time. There is something about it that is missing from the rather theoretical treatment often given this subject by the psychologist, psychiatrist or sociologist. Part II deals with problems of war and peace in an interesting way. The author develops the picture of man as a fighting animal,

states that ". . . instinct in man as in animals yields only to force", and that there must be a high command to preserve international order. He uses the organization of body cells to support his belief that mutual dependence, mutual coöperation, and an organ of control are essential to peace, which he defines as organic health. The latter part of this book contains a good deal of homespun philosophy which is thoughtful but, to this reader, somewhat lacking in recognition of the contributions which have been made by the social sciences to the understanding of problems which are discussed. For example, Dr. Needham says, "Men and nations fight, as do animals, when well armed, well fed, well conditioned generally, and when there is nothing much worthwhile to fight about."

Modern social thinkers would be inclined to believe that we could always find that there was something to fight about, were we capable of understanding it, and much work has been done in an effort to study the relationship between aggression and the frustrations of our culture. Dr. Needham hints at this, but does not discuss it with the same authority and clarity which he demonstrates in the first part of the book.

"About Ourselves" should serve as a useful "refresher" for those who have become immersed in advanced work in any of the biological or sociological fields. It should also be valuable as orientation reading for the layman or for college students.

H. W. N.

The Vitamins in Medicine. By FRANKLIN BICKNELL, D.M., M.R.C.F., and FREDERICK PRESCOTT, M.Sc., Ph.D., A.R.I.C., M.R.C.S., Clinical Research Director, The Wellcome Foundation, London. Second Edition. 23.5 × 16 cm. 1946. Grune and Stratton, New York City. Price, \$12.00.

The second edition of "The Vitamins in Medicine" follows the first within four years. The marked advances in knowledge in this field have been particularly noticeable in the studies on the B complex. Twenty-two members have now been identified either as chemical entities or by their biological effect on various experimental animals. These advances have necessitated a complete revision of the section on these vitamins. It has been pointed out that a number of the vitamins of the B complex which have been characterized only by their biological activity may prove to be identical with some of the known factors of the B complex or mixtures of known amino acids, so that ultimately the number of factors may be decreased. The author presents a useful chart showing the chronological resolution of the B complex into its various fractions.

Two new chapters have been added on the unsaturated fatty acids and the minor fat soluble vitamins. It has been pointed out that the designation of the so-called essential fatty acids (linoleic, linolenic, and arachidonic) is somewhat ambiguous since any one of these acids can replace the other two in the diet. The only condition in which these acids appear to be important is in eczema.

The vitamin tables have been revised in the light of recent standards. Units are given where possible in micrograms or milligrams as well as in international units. When other units are in use the conversion factors are also presented if possible.

The authors have covered the clinical literature very thoroughly and have included over 4,500 references. The volume is exceptionally well indexed. It is one of the most complete works in this field that has been published and is an exceptional reference volume.

M. A. A.

Mental Health in College. By CLEMENTS C. FRY, M.D., with the collaboration of EDNA G. ROSTOW. 395 pages; 23.5 × 15.5 cm. The Commonwealth Fund, N.Y.C. 1942. Price, \$2.00.

After ten years of experience, from 1926 to 1942, the authors have described and evaluated the psychiatric service offered to students of Yale University by the Division of College Psychiatry and Mental Hygiene, of the Department of University Health. In common with all other types of psychiatric service, this mental health program has encountered in educators, parents, patients and others, attitudes of indifference, popular prejudice, specific objections and the usual conviction that all that is needed to solve mental health problems is a generous application of "good common sense." Of the 1257 Yale students receiving psychiatric service, 787 were undergraduates, with 45 per cent coming from the freshman class, and the remaining 470 were enrolled in the Graduate School and the Schools of Fine Arts, Divinity, Law, Medicine, Nursing, Music and Forestry. As a group, these patients constituted a cross-section of the university population, including "Phi Beta Kappa and low-stand students; rich and poor; socially prominent and the reverse; the varsity athletes and the unathletic; senior society and fraternity members, and those who do not belong to any special groups."

In 1141 of the cases studied and treated, "these students looked upon themselves and were regarded by others as 'normal people,' but they reacted at times in much the same way as so-called 'abnormal' patients." Responding to stresses in separation from homes and families and adjustment to college demands during "a period usually coinciding with the climax of adolescent changes in their physical, impulsive, emotional and intellectual lives," these students developed behavior disorders, gastrointestinal upsets, fatigue, insomnia and periods of anxiety and depression. Psychoses and other serious psychopathies were encountered in 116 students, or 8 per cent of the case load. Even among these, a considerable number recovered after a time and completed their college course. Fifty-three per cent of the students were seen from one to three times by the psychiatrist, while the remaining 47 per cent were interviewed more or less regularly for a month, several months or years.

In the area of family relationships, emotional conflicts may arise in attempts to grow up and achieve independence in the face of pressures and demands by dominating parents, parents who desire to absorb, possess and supervise their sons, or who have abnormal attachments to them. Friction between parents in the home, or separated parents, rejection by parents and other vicissitudes or crises in family life may markedly affect students' personalities and college adjustments. The students are also emotionally engaged with problems of sexual growth, behavior and attitudes. Difficulties in this area were related to petting, masturbation, heterosexual experimentation, promiscuity, adjustments in courtship or marriage, fears of homosexuality and homosexual activities. Because "the community limits the dissemination of proper information, tolerates the spread of false notions and inculcates a fear of sex," the student's view of sex "is compounded of misinformation and taboo." The consequent "feelings of inferiority, of alarm, of guilt, of shame, of depression, and of anxiety—may be intensified by ignorance, often with serious consequences."

For many entering students, emotional problems develop in relation to the demand for scholastic success. Lack of ability or ambition, inadequate scholastic training and preparation for independent work, the demands and pressures exerted by families, financial handicaps, social maladjustment or over-valuation of social success and other personality problems play an important rôle in academic failures. Upper-classmen and graduates may also face failures for similar or related reasons. In relation to problems of social adjustment in the college society, the authors state

that "recognition, acceptance, and approval by the group are, of course, the social objective of all students, for such acceptance represents a long step, in any society, toward security for most individuals," and "social success cannot be under-estimated in any consideration of the college community." Boys who are handicapped by self-consciousness, shyness and social awkwardness, by previous experience of protected absorption in family life, by rejection by the family, by differences in social background and lack of social experience, financial pressure and other personality handicaps, often develop emotional upsets and mental health problems.

Although some cases are presented in considerable detail, many seem sketchy and the value of this book lies more in the general discussion of the varied mental health problems of college students. Separate presentation of the problems of freshmen, upperclassmen and graduate students leads to considerable overlapping and repetition. The book, however, will be of great value to all those engaged in the education and guidance of youth in high schools, colleges and universities, and to physicians, parents and others who are interested in the treatment and prevention of problems of adjustment among these age groups.

C. B.

Alterações Hepáticas na Tireotoxicose. By P. A. DA COSTA COUTO. 278 pages; 23.5 × 16 cm. 1944. Borsoi, Rio de Janeiro.

This monograph is based on a three year study of hepatic changes noted in hyperthyroidism. The literature is thoroughly reviewed and the bibliography complete. The author is not impressed by jaundice, reported by others as a common feature in thyrohepatic disturbances. The Quick hippuric acid synthesis test and the Bauer galactose tolerance test uniformly indicated liver cell function disturbance. Thus the mechanisms disturbed were the "antitoxic" and glycogen storage.

A correlation between the thyroid and liver is generally recognized, but no signal evidence of this relationship outside of jaundice which occurs uncommonly is identifiable in the clinical picture of hyperthyroidism. Widespread hepatic lesions occur in the severe types of thyroid dysfunction. There is a direct correlation between the severity of the symptoms and the underlying endocrine and metabolic disturbances.

The necropsy findings in two instances of hyperthyroidism are described. These conform to other published accounts. Congestive changes in the liver sinusoids and cellular changes approaching necrosis are well illustrated. Similar lesions occurring in guinea pigs poisoned with thyroid substance or thyroxin are also reproduced excellently.

Great significance is attached to the hepatic status in fatal Graves' disease or thyroid storm. Analogy is made to the hepatorenal syndrome.

The recognition of the thyrohepatic correlation is necessary, in the author's opinion, for therapeutic orientation, both in the pre- and post-operative periods of hyperthyroidism.

da Costa Couto recommends a regimen which restores the functional equilibrium of the liver. Carbohydrate, liver extract and vitamins A, B, and C are among these measures.

No new data appear in this extensive monograph. The material presented is well handled. The unqualified stand on the importance of hepatic dysfunction in thyroid storm is not supported by proved data. The emphasis on joint treatment of thyroid and hepatic dysfunction in all phases of hyperthyroidism is the commendable theme of this work.

S. S. L.

BOOKS RECEIVED

Books received during July are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

- The Venereal Diseases.* By JAMES MARSHALL, M.B., B.S., M.R.C.S. 348 pages; 22 × 14.5 cm. 1946. The Macmillan Company, New York. Price, \$4.50.
- Anesthesia in General Practice.* By S. C. CULLEN, M.D. 259 pages; 21 × 14.5 cm. 1946. Year Book Publishers, Inc., Chicago. Price, \$3.50.
- Peptic Ulcer; Its Diagnosis and Treatment.* By I. W. HELD, M.D., and A. ALLEN GOLDBLOOM, M.D. 382 pages, 25 × 16.5 cm. 1946. Charles C. Thomas, Springfield, Ill. Price, \$6.50.
- The Endeavor of Jean Fernel.* By Sir CHARLES SHERRINGTON, O.M. 223 pages; 22.5 × 14.5 cm. 1946. Cambridge University Press, The MacMillan Company. New York. Price, \$3.50.
- The Child from Five to Ten.* By ARNOLD GESELL, M.D., Director Yale Clinic of Child Development, and FRANCIS L. ILG, M.D., Asst. 475 pages; 25.5 × 18.5 cm. 1946. Harper & Brothers, New York. Price, \$4.00.
- Currents in Biochemical Research.* Edited by DAVID E. GREEN. 486 pages; 24 × 16.5 cm. 1946. Interscience Publishers, Inc., New York. Price, \$5.00.
- Mother and Baby Care in Pictures.* Third Edition. By LOUISE ZABRISKIE. 203 pages; 23.5 × 16 cm. 1946. J. B. Lippincott Company, Philadelphia. Price, \$2.00.
- The American Hospital.* By E. H. L. CORWIN, Ph.D. 226 pages; 21.5 × 14 cm. 1946. The Commonwealth Fund; New York. Price \$1.50.
- Urologic Roentgenology.* Second Edition Revised. By MILEY B. WESSON, M.D. 259 pages; 24 × 15 cm. 1946. Lea & Febiger, Philadelphia. Price, \$5.50.
- Narco-Analysis.* By J. STEPHEN HORSLEY. 134 pages; 19 × 13 cm. 1946. Oxford University Press, New York. Price, \$2.50.
- Lippincott's Quick Reference Book for Medicine and Surgery.* Thirteenth Edition. By GEORGE E. REHBERGER, A.B., M.D. 1461 pages; 26 × 18 cm. 1946. J. B. Lippincott Company, Philadelphia. Price, \$15.00.

COLLEGE NEWS NOTES

NEW LIFE MEMBERS OF THE COLLEGE

The College is gratified to announce the following additional Life Members listed in the order of subscription:

Dr. Morris Deitchman, Youngstown, Ohio
Dr. George Foster Herben, Yonkers, N. Y.
Dr. Arthur Ernest Moon, Temple, Tex.
Dr. Gustav L. Kaufmann, Chicago, Ill.

GIFTS TO THE COLLEGE LIBRARY

The following gifts of publications by members are gratefully acknowledged:

Dr. G. S. Backenstoe, (Associate), Emmaus, Pa.—4 reprints
Dr. Arthur Bernstein, F.A.C.P., Newark, N. J.—1 reprint
Dr. Louis F. Bishop, Jr., F.A.C.P., New York, N. Y.—1 reprint
Dr. Robert G. Bloch, F.A.C.P., Chicago, Ill.—7 reprints
Dr. Benjamin Burbank, F.A.C.P., Brooklyn, N. Y.—5 reprints
Dr. Nathan Smith Davis, III, F.A.C.P., Chicago, Ill.—13 reprints
Dr. Herbert R. Edwards, F.A.C.P., New York, N. Y.—13 reprints
Dr. William E. Jahsman, F.A.C.P., Ferndale, Mich.—1 reprint
Dr. Samuel R. Kaufman, F.A.C.P., Wilkes-Barre, Pa.—1 reprint
Dr. William David King, F.A.C.P., Phoenix, Ariz.—1 reprint
Dr. Rudolph A. Kocher, (Associate), Carmel, Calif.—1 reprint
Dr. Emanuel Klosk, (Associate), Newark, N. J.—1 reprint
Dr. Thomas H. McGavack, F.A.C.P., New York, N. Y.—5 reprints
Dr. Samuel Millman, F.A.C.P., Brooklyn, N. Y.—2 reprints
Dr. Edward W. Miskall, F.A.C.P., East Liverpool, Ohio—1 reprint
Dr. William J. O'Connel, Jr., (Associate), East Providence, R. I.—1 reprint
Dr. B. M. Overholt, F.A.C.P., Knoxville, Tenn.—1 reprint
Dr. Aaron E. Parsonnet, F.A.C.P., Newark, N. J.—1 reprint
Dr. Merritt H. Stiles, F.A.C.P., Spokane, Wash.—6 reprints
Dr. Leon N. Sussman, (Associate), New York, N. Y.—1 reprint
Dr. Harry Warshawsky, (Associate), Dayton, Ohio—1 reprint
Dr. Alexander Wiener, F.A.C.P., Brooklyn, N. Y.—13 reprints
Dr. I. Milton Wise, F.A.C.P., Mobile, Ala.—4 reprints
Dr. Andrew C. Woofter, F.A.C.P., Parkersburg, W. Va.—3 reprints
Dr. Paul H. Wosika, (Associate), Chicago, Ill.—5 reprints

The College further acknowledges with deep gratitude the receipt of a complete set of the American Journal of the Medical Sciences from its inception, the gift being made by Dr. Louis F. Bishop, Jr., F.A.C.P., of New York City. This journal was originally collected and owned by Dr. Bishop's father, the late Louis Faugeres Bishop, F.A.C.P., and is added to the College Library as a memorial to him. This rare set of this journal will prove increasingly valuable as the years go by.

The Nineteenth Graduate Fortnight of the New York Academy of Medicine will occur October 7-18, 1947. The subject of the program will be Tumors. The

program will consist in morning panel discussions, afternoon hospital clinics, evening addresses, scientific exhibits and demonstrations. Registration cards will be supplied to Fellows of the Academy without charge, and medical officers engaged in active service will not be required to register. All others may receive registration cards upon payment of a fee of \$5.00.

Dr. Charles L. Brown, F.A.C.P., Professor and Head of the Department of Medicine of the Temple University School of Medicine, will assume the duties of Dean of the Hahnemann Medical School and Hospital of Philadelphia, September 1. Dr. Brown received his medical degree at the University of Oklahoma School of Medicine and is a Diplomate of the American Board of Internal Medicine. He has held appointments in the Peter Bent Brigham Hospital and the Children's Hospital, Boston, and in the Harvard Medical School and the University of Michigan School of Medicine. Dr. Brown is a Fellow of the American Association for the Advancement of Science and of the American Medical Association. Among the societies of which he is a member are the American Society for Clinical Investigation, the Central Society for Clinical Research, the Physiological Society of Philadelphia, and the American Heart Association.

Dr. George C. Wilson, F.A.C.P., has accepted appointment as Assistant Chief of the Tuberculosis Division Branch No. 1, Veterans Administration, Boston, Mass. Formerly a resident of Norwich, Conn., Dr. Wilson has removed to Waban, Mass.

Announcement has been received of the Seventh Annual Congress on Industrial Health, which will be held September 30–October 3, 1946, at the Copley-Plaza Hotel, Boston, Mass. The sponsor of the Congress is the Council on Industrial Health of the American Medical Association.

Dr. Francis R. Dieuaide, F.A.C.P., who recently became scientific director of the Life Insurance Medical Research Fund, formerly a resident of Boston, Mass., may henceforth be addressed in care of the Fund at 2 E. 103rd St., New York 29, N. Y.

The Sixth Annual Session of the American Diabetes Association was held September 16–18, 1946, in Toronto, Ont., Can. Drs. Joseph H. Barach, F.A.C.P., Pittsburgh, and R. M. Wilder, F.A.C.P., Rochester, Minn., president and incoming president, respectively, of the Association, presided over the sessions.

The program of the first day commemorated the twenty-fifth anniversary of the discovery of insulin. Among the speakers of the day were Drs. David P. Barr, New York, President of the American College of Physicians; Seale Harris, F.A.C.P., Birmingham; E. P. Joslin, F.A.C.P., Boston; and R. M. Wilder.

The second day's program concerned the accomplishments of the past twenty-five years. Papers were presented by Drs. Frank N. Allan, F.A.C.P., Boston; F. B. Peck, F.A.C.P., Indianapolis; I. M. Rabinowitch, F.A.C.P., Montreal; and Priscilla White, F.A.C.P., Boston.

The third day featured reports of recent investigative work and an open forum.

Dr. Ben E. Grant, F.A.C.P., formerly of Los Angeles, Calif., has accepted appointment as Chief Medical Officer of the Veterans Administration Hospital, Vancouver, Wash.

Dr. Samuel J. Prigal, (Associate), New York, was awarded the Merrit H. Cash Prize for 1946 by the Medical Society of the State of New York, for his essay entitled: "Studies with Medicated Aerosols: The Use of the Lungs as a Portal for the Introduction of Therapeutic Agents for Systemic Effects".

The Medical Consultants Division of the Office of the Surgeon General, Colonel Arden Freer, F.A.C.P., Director, has announced the appointment of sixteen civilian physicians as consultants in internal medicine to the Secretary of War. Of these, thirteen are Fellows, and one an Associate of the College. They are: Dr. E. V. Allen, Rochester, Minn.; Dr. Worth B. Daniels, Washington, D. C.; Dr. George B. Denney, Boston, Mass.; Dr. Eugene P. Eppinger, Boston, Mass.; Dr. Joseph M. Hayman, Jr., Cleveland, Ohio; Dr. Walter B. Martin, Norfolk, Va.; Dr. John Minor, Washington, D. C.; Dr. Hugh J. Morgan, Nashville, Tenn.; Dr. William T. Rainey, Fayetteville, N. C.; Dr. George P. Robb, Washington, D. C.; Dr. Monroe J. Romansky, (Associate), Silver Spring, Md.; Dr. Virgil Sydenstricker, Augusta, Ga.; Dr. Henry M. Thomas, Jr., Baltimore, Md.; Dr. Irving S. Wright, New York, N. Y.

Dr. John Minor, F.A.C.P., Washington, D. C., has been awarded the Legion of Merit. The award was made in recognition of Dr. Minor's services while Colonel in the Medical Corps, AUS, as Medical Consultant to the Surgeon of the Third Service Command. The announcement of this award contained the following statement: "He raised the professional standards of the various hospitals of this command to a high degree of efficiency by his leadership and exceptional professional ability".

Dr. Philip K. Arzt, (Associate), Jamestown, has been elected to the position of president-elect of the North Dakota State Medical Association.

Drs. Hugh B. Campbell, F.A.C.P., Norwich, Conn., and Horton C. Hinshaw, F.A.C.P., Rochester, Minn., have been elected Vice Presidents of the National Tuberculosis Association. Dr. Herbert R. Edwards, F.A.C.P., New York, has been elected Secretary of the association.

Dr. James M. MacMillan, (Associate), formerly of Detroit, has moved to Richmond, Va., and will be associated there in the practice of internal medicine, particularly gastro-enterology, with Dr. Charles M. Caravati, F.A.C.P.

Recent appointments as consultants to the Richmond Branch Medical Service of the Veterans Administration included Drs. Dean B. Cole, F.A.C.P., and R. F. Gayle, F.A.C.P., of Richmond, Va., the former as consultant in tuberculosis and the latter as consultant in neuropsychiatry. Dr. Benjamin M. Baker, Jr., F.A.C.P., Baltimore, Md., received appointment as consultant in internal medicine.

Advance information received concerning the program for the 1946 meeting of the Mississippi Valley Medical Society gives the following Fellows of the College as speakers: Drs. Robert E. Britt, G. O. Broun, Ralph A. Kinsella, LeRoy Sante, and W. Barry Wood, Jr., all of St. Louis; M. Herbert Barker, Robert S. Berghoff, and Israel Davidsohn, all of Chicago; and H. Corwin Hinshaw, Rochester, Minn. The meeting will take place at the Hotel Jefferson, St. Louis, September 25-27. Dr. Harold Swanberg is secretary of the society.

Dr. Edward Weiss, F.A.C.P., Philadelphia, addressed the medical section of the American Life Convention at its meeting June 20 at Hot Springs, Va., on the subject, "Psychosomatic Aspects of Chronic Disease".

Dr. George Morris Piersol, Secretary General of the American College of Physicians, has been elected Vice President of the Pennsylvania Academy of Physical Medicine for the year 1946-47.

SCHENLEY INSTITUTE AWARDS FELLOWSHIPS

The Schenley Research Institute, which is affiliated with Schenley Distillers Corporation and Schenley Laboratories, Inc., has announced an allocation of \$110,000 to support a number of three-year postgraduate fellowships to be awarded by the University of Wisconsin. It is the plan of the Institute and of the University that these fellowships shall be for the conduct of basic scientific research in the field of production and mode of action of antibiotics. The stipends will be of the order of \$3,600 to \$4,000 a year and, in addition, the Institute will provide the University with allowances for the research expenses of the Fellows. The Fellows will work under the supervision of members of the University's Departments of Agriculture, Bacteriology, Biochemistry, Plant Pathology, Veterinary Science and Botany.

Dr. Henry R. Carstens, F.A.C.P., Philadelphia, Director of Medical Service, Veterans Administration, Branch No. 3, has announced that by agreement among the Army, Navy and Veterans Administration, 41 Army and Navy physicians will soon report for duty in Veterans Hospitals in Pennsylvania, New Jersey and Delaware.

Dr. John D. Davis, F.A.C.P., retired from the Army of the United States with the rank of Colonel, and has accepted an appointment as Chief of the Chest Diseases Service, and Chief of the Medical Service, in the Veterans Administration at Birmingham General Hospital, Van Nuys, Calif.

Brigadier General William L. Hart, U.S.A., Retired, F.A.C.P., Washington, D. C., has been appointed Dean of the Southwestern Medical College, Dallas, Tex. Dr. Hart assumed this position on August 1, succeeding Dr. Tinsley R. Harrison, F.A.C.P. Dr. Harrison will continue to serve the College as Professor of Internal Medicine.

Dr. William S. Middleton, F.A.C.P., Madison, Wis., has been made an Honorary Fellow of the Royal Society of Medicine.

The formation of an Antibiotic Study Section has been announced by the National Institute of Health, Bethesda, Md. The following Fellows of the College have been made members of the section: Dr. David P. Barr, New York; Capt. George B. Dowling, Washington, D. C.; Dr. W. Barry Wood, Jr., St. Louis, Mo.

Schering Corporation, Bluefield, New Jersey, has announced that it will send to interested physicians, upon request, a portfolio of illustrations by the noted artist, Rockwell Kent, of patients suffering from specific endocrine deficiencies.

Dr. Clarence E. de la Chapelle, F.A.C.P., New York, has been appointed Associate Dean of the New York University College of Medicine. Dr. de la Chapelle has held the positions of Professor of Clinical Medicine, Assistant Dean, and Director of the Postgraduate Division of the College of Medicine.

The Distinguished Service Medal of the American Medical Association has been awarded to Dr. Anton J. Carlson, F.A.C.P., Chicago, Ill. This tribute to Dr. Carlson, long an active member of the faculty of the University of Chicago, and of the American College of Physicians and the American Medical Association, recognizes Dr. Carlson's outstanding services to medical research and to medicine.

Drs. Jack C. Norris, F.A.C.P., Atlanta, and Ernest F. Wahl, F.A.C.P., Thomasville, have been appointed by Governor Arnall of Georgia to membership on a board to determine medical questions pertaining to workmen's compensation.

Dr. A. C. Ivy, F.A.C.P., Chicago, has been appointed to succeed Dr. Raymond V. Allen, F.A.C.P., as Vice President in charge of the Colleges of Medicine, Dentistry and Pharmacy, and hospitals and institutes of the University of Illinois in Chicago. Dr. Ivy has also been appointed to the position of Distinguished Professor of Physiology in the University's Graduate School. Dr. Ivy has served with distinction the Northwestern University Medical School, in which he has held since 1925 the title of Nathan Smith Davis Professor of Physiology and Pharmacology. During World War II, Dr. Ivy was Director of the Naval Medical Research Institute, Bethesda, Md., and served also as consultant to the War and Navy Departments.

Dr. Robert O. Brown, F.A.C.P., is the recipient of a citation of merit awarded by alumni of the University of Chicago on June 8.

Dr. Alonzo Frederick Brand, F.A.C.P., has been commissioned in the regular corps of the U. S. Public Health Service with the rank of Senior Surgeon and is now the Venereal Disease Control Adviser for the Philippines. Dr. Brand previously held a commission as Lieutenant Colonel and was assigned to the U. S. Public Health Service Reserve.

Dr. Harold J. Kullman, F.A.C.P., recently assumed a full time position as Chief of Medical Service at the Veterans Administration Hospital, Dearborn, Mich.

CAPTAIN CERES RECEIVES LEGION OF MERIT

Captain Frederick Ceres, (MC), USN, F.A.C.P., received the Legion of Merit with the following citation from Admiral Chester W. Nimitz, Commander-in-Chief of the U. S. Pacific Fleet:

Citation:

"For exceptionally meritorious service in a position of great importance and responsibility as Medical Officer in Command of the U. S. Naval Hospital, Aiea Heights, Territory of Hawaii, from 2 August 1943 to 4 July 1944. He personally supervised the extensive expansion his command required for the hospitalization of

the large numbers of wounded from combat areas in the Central Pacific, thereby contributing materially to the rapid rehabilitation of personnel essential to successful prosecution of the war against Japan. During this entire period, he habitually displayed sound judgment, tireless energy, zeal, and initiative, thereby succeeding in developing and maintaining his hospital as the outstanding institution of its kind in this area. Throughout his tour of duty in the Fourteenth Naval District, Captain Ceres has maintained the highest standards of efficiency and morale within his command in keeping with the finest traditions of the naval service."

APPOINTMENTS OPEN

A Fellow of the American College of Physicians who is now superintendent of a large State Hospital in Kentucky, has applied to the College to refer to him some competent young man of character and ability who desires work in neuropsychiatry. The hospital is a modern institution, ideally situated and there are several openings. Any interested physicians should communicate with the Executive Secretary of the College, Mr. E. R. Loveland, 4200 Pine Street, Philadelphia 4, Pa., making reference to "AO-3."

Dr. Thomas T. Mackie, F.A.C.P., formerly of New York City, has accepted an appointment as Professor of Preventive Medicine and Chairman of the Division of Medicine at the Bowman Gray School of Medicine, Winston-Salem, N. C. Dr. Mackie recently returned from England. He served during World War II as a Colonel in the Army. He is President of the American Foundation for Tropical Medicine.

NAVAL CITATION TO DR. DAR D. STOFER, F.A.C.P.

Dr. Dar D. Stofer, F.A.C.P., now of Monterey, Calif., received toward the end of his Naval service in April, 1946, the following citation from the Surgeon General of the U. S. Navy. Dr. Stofer was a Captain in the Naval Reserve:

"Your outstanding performance of duty as a medical officer on duty at U. S. Naval Mobile Hospital No. 6 in New Zealand, is considered worthy of special commendation.

"Your superior professional qualifications in internal medicine, and your sustained interest, diligence and coöperation as Chief of the Medical Service made possible a thorough medical study of all neuro-psychiatric cases in the hospital and, by the elimination of organic disease, contributed largely to the successful treatment and return to combat of an unusually high percentage of neuroses and combat fatigue patients.

"I commend you for exceptional ability, resourcefulness and outstanding devotion to duty which reflected credit upon yourself and the Naval Service."

Capt. Julian Love, (MC), USN, F.A.C.P., was stationed at Kwajalein, Marshall Islands, during the atomic bomb tests at Bikini, and witnessed the B bomb experiment from a 7500' altitude on a plane, some seven miles slant range from the target.

The Twenty-Fourth Annual Fall Clinical Conference of the Kansas City Southwest Clinical Society will occur October 7-10, 1946, at the Municipal Auditorium, Kansas City, Mo. Among the speakers at the sessions will be Dr. Charles A. Doan, F.A.C.P., Columbus, Ohio; Dr. Tinsley R. Harrison, F.A.C.P., Dallas, Tex.; and Walter L. Palmer, F.A.C.P., Chicago, Ill.

Dr. Edwin C. Swift, F.A.C.P., Jacksonville, has been elected Vice President of the Florida Medical Association.

Dr. Benjamin B. Souster, F.A.C.P., St. Paul, Minn., has become Secretary of the Minnesota State Medical Association.

Dr. James B. Bullitt, F.A.C.P., Chapel Hill, retired on June 5 from the faculty of the University of North Carolina School of Medicine. Dr. Bullitt was a member of the faculty for thirty-three years.

Dr. Morgan Cutts, F.A.C.P., Providence, has been elected Secretary of the Rhode Island Medical Society.

The American Public Health Association has announced the formation of a Committee to recommend awards for outstanding achievements in research and in the application of research dealing with diseases which constitute the major causes of death. The awards will be made available by the Albert B. and Mary Lasker Foundation. Each year the awards will consist of four gifts of \$1000 and commemorative statuettes; especially significant contributions will be acknowledged by an additional award of \$2500. The Committee includes the following Fellows of the College: Dr. George Baehr, Dr. Robert F. Loeb, Dr. Hugh R. Leavell, all of New York; Dr. Thomas Parran, Washington; Dr. James S. Simmons, Boston.

In the July News Notes, the rank at time of separation from service of Dr. Horst A. Agerty was incorrectly given as 'Captain.' Dr. Agerty held the rank of 'Major' at time of separation.

Dr. J. A. C. Gray, F.A.C.P., New York, formerly commissioned in the Medical Corps, USNR, has accepted a commission in the Medical Corps of the USN.

The 1947 Assembly of the New Orleans Graduate Clinical Assembly will be held in the Municipal Auditorium, New Orleans, February 24-27, 1947.

Dr. John W. Ferree, F.A.C.P., formerly of Indianapolis, has become Director of the Division of Education and Special Projects of the American Social Hygiene Association. Dr. Ferree's office is located at 1790 Broadway, New York, N. Y., and he will reside at 21 Guion St., Pleasantville, N. Y.

The 1946 Sessions of the Omaha Mid-West Clinical Society will occur October 28 to November 1, 1946, inclusive.

Dr. George Cupp Griffith, Lt. Comdr., (MC), USN, Ret'd., F.A.C.P., Philadelphia, has received the commendation of the Surgeon General of the U. S. Navy. The citation included the following statement:

"Exercising unusual professional skill and energy you were, in a large part, responsible for the efficient functioning of the rheumatic fever unit at the Naval Hospital, Corona, Calif."

Dr. Henry A. Schroeder, F.A.C.P., who recently was separated from the Naval Reserve, is now Associate Professor of Medicine at Washington University School of Medicine, and Assistant Visiting Physician at Barnes Hospital, St. Louis. He was formerly Associate of the Rockefeller Institute.

A.C.P. POSTGRADUATE COURSES INCREASE IN DEMAND

Although the Committee on Postgraduate Courses has more than doubled the number of courses for the autumn of 1946, the demand continues to exceed the facilities. Already several courses are oversubscribed, namely:

Course No. 1—Internal Medicine—University of Pittsburgh School of Medicine
 Course No. 2—Psychosomatic Medicine—University of Colorado School of Medicine
 Course No. 8—Cardiology—Massachusetts General Hospital
 Course No. 13—Cardiology—University of Michigan Medical School

At the date this news item is prepared, August 23, 1946, all other courses are open, although the registration is rapidly mounting. All members received copies of the Postgraduate Bulletin early in August. One should not delay to file application because it is believed that practically all courses will be filled to capacity.

The Committee on Postgraduate Courses is already working on the schedule of courses for the spring of 1947. The following courses appear on the proposed schedule and others will be added:

Cardiovascular Disease—Northwestern University, Chicago, Ill.—Dr. J. Roscoe Miller, F.A.C.P., Director
 Cardiovascular Disease—Emory University School of Medicine, Atlanta, Ga.—Dr. Bruce Logue, F.A.C.P., Director
 Internal Medicine—University of Cincinnati School of Medicine, Cincinnati, Ohio—Dr. M. A. Blankenhorn, F.A.C.P., Director
 Physical Medicine—University of Pennsylvania, Philadelphia, Pa.—Dr. George Morris Piersol
 Tissue Growth and Tumors—Wanamaker Foundation, Lankenau Hospital, Philadelphia, Pa.—Dr. Stanley Reimann, F.A.C.P. and Dr. Edward L. Bortz, F.A.C.P., Directors

Still other courses under consideration include Diseases of the Chest, Neuropsychiatry, Pathology, Peripheral Vascular Diseases, and additional courses in Internal Medicine.

Copies of the Postgraduate Bulletin for Autumn 1946 Courses and for Spring 1947 are or will be obtainable by request to the Executive Secretary, American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

RETIREMENTS FROM SERVICE

Since the last publication of this journal, the following members of the College have been reported retired or on terminal leave (to August 12, 1946 inclusive).

Stanton T. Allison, New York, N. Y. (Capt., MC, USNR)

John H. Baird, Washington, D. C. (Col., MC, AUS)

Lyle A. Baker, Hines, Ill. (Lt. Col., MC, AUS)

Roland W. Banks, Yeadon, Pa. (Major, MC, AUS)

Walter M. Bartlett, Benton Harbor, Mich. (Col., MC, AUS)

Gerald Blankfort, Little Rock, Ark. (Major, MC, AUS)
James E. Bovaird, Wolfeboro, N. H. (Capt., MC, AUS)
Norman H. Boyer, Boston, Mass. (Capt., MC, AUS)
Stewart F. Brewen, Wormleysburg, Pa. (Capt., MC, AUS)
Timothy F. Brewer, Hartford, Conn. (Lt. Comdr., MC, USNR)
Paul H. Burgert, Lake Forest, Ill. (Capt., MC, AUS)

Henry Caplan, Meriden, Conn. (Capt., MC, AUS)
William Chester, Mamaroneck, N. Y. (Lt. Col., MC, AUS)
Henry L. Cooper, Denver, Colo. (Major, MC, AUS)
William D. Coventry, Duluth, Minn. (Major, MC, AUS)

Worth B. Daniels, Washington, D. C. (Col., MC, AUS)
Thomas H. DeLaureal, Lake Charles, La. (Major, MC, AUS)

Robert W. Elliott, St. Louis, Mo. (Major, MC, AUS)
Clayton B. Ethridge, Washington, D. C. (Lt. Comdr., MC, USNR)

Thomas J. Fatherree, Soap Lake, Wash. (Comdr., MC, USNR)
Lucian M. Ferris, Vicksburg, Miss. (Lt. Col., MC, AUS)
Elmer Friedland, Buffalo, N. Y. (Major, MC, AUS)

J. Richard Gott, Jr., Murfreesboro, Tenn. (Comdr., MC, USNR)

Paul V. Hamilton, Cincinnati, Ohio (Lt. Col., MC, AUS)
Robert M. Harris, Miami, Fla. (Comdr., MC, USNR)
Thomas G. Hobbs, Chicago, Ill. (Major, MC, AUS)
Joseph F. Hughes, Philadelphia, Pa. (Comdr., MC, USNR)

Archibald D. Kennedy, Louisville, Ky. (Major, MC, AUS)
J. Allen Kennedy, Nashville, Tenn. (Major, MC, AUS)
Richard J. Killhullen, Wilkes-Barre, Pa. (Major, MC, AUS)
Joseph R. Kriz, New Orleans, La. (Col., MC, AUS)

Howard J. Lee, Oshkosh, Wis. (Lt. Col., MC, AUS)
Jerome S. Levy, Little Rock, Ark. (Lt. Col., MC, AUS)
Philip H. Livingston, Chattanooga, Tenn. (Lt. Col., MC, AUS)
Louis Lowenstein, Montreal, Que., Can. (Wing Comdr., RCAF)
Joseph M. Lubitz, Chicago, Ill. (Lt. Comdr., USPHS (R))
Edgar H. Lutz, Montrose, Pa. (Capt., MC, AUS)

A. Seldon Mann, Alton, Ill. (Lt. Col., MC, AUS)
Donald F. Marion, Detroit, Mich. (Lt. Col., MC, AUS)
George C. McEachern, Forest Hills, N. Y. (Lt. Col., MC, AUS)
Harold P. McGan, Albany, N. Y. (Lt. Col., MC, AUS)
James A. McLaughlin, Ocean Bluff, Mass. (Lt., MC, USNR)
Robert J. Mearin, Syracuse, N. Y. (Lt. Comdr., MC, USNR)
Ralph W. Mendelson, Albuquerque, N. M. (Lt. Col., MC, AUS)
Frank Meyers, Buffalo, N. Y. (Lt. Col., MC, AUS)
Saul Michalover, Brooklyn, N. Y. (Col., MC, AUS)

Walter C. Nalty, Fort Bayard, N. M. (Lt. Col., MC, AUS)
Jack C. Norris, Atlanta, Ga. (Capt., MC, USNR)

Abraham Penner, New York, N. Y. (Lt. Col., MC, AUS)
Thornton T. Perry, III, Rochester, Minn. (Lt., MC, AUS)
Lee T. Pruitt, Beaumont, Tex. (Col., MC, AUS)

Alexander Sanders, Chicago, Ill. (Major, MC, AUS)
 Henry A. Schroeder, New York, N. Y. (Comdr., MC, USNR)
 George Schwartz, New York, N. Y. (Capt., MC, AUS)
 J. Dunbar Shields, Jr., Concord, N. H. (Lt., MC, USNR)
 Donald G. Stannus, Miami Beach, Fla. (Major, MC, AUS)
 Irwin D. Stein, Mt. Vernon, N. Y. (Capt., MC, AUS)
 Charles F. Sweigert, San Francisco, Calif. (Lt. Col., MC, AUS)

David S. Traub, Louisville, Ky. (Capt., MC, AUS)

Robert A. Ullman, Buffalo, N. Y. (Capt., MC, AUS)

Stoughton R. Vogel, Philadelphia, Pa. (Major, MC, AUS)

William von Stein, New York, N. Y. (Major, MC, AUS)

Richard Wagner, Elizabeth, N. J. (Capt., MC, AUS)

Edmund F. Walker, Worcester, Mass. (Major, MC, AUS)

Edgar Wayburn, San Francisco, Calif. (Major, MC, AUS)

Zolton T. Wirtschafter, Cleveland, Ohio (Lt. Col., MC, AUS)

Ellis W. Young, Pittsburgh, Pa. (Capt., MC, AUS)

MINUTES OF THE BOARD OF REGENTS

PHILADELPHIA, PA.

MAY 12, 1946

The first meeting of the Board of Regents during the Philadelphia Annual Session was held at Convention Hall, Sunday, May 12, 1946, at two o'clock, with the President, Dr. Ernest E. Irons, presiding, Mr. E. R. Loveland acting as Secretary, and with the following in attendance:

Doctors David P. Barr; William D. Stroud; James J. Waring; George Morris Piersol; Christopher C. Shaw; T. Homer Coffen; Jonathan C. Meakins; Hugh J. Morgan; Francis G. Blake; James F. Churchill; Reginald Fitz; Roger I. Lee; Charles T. Stone; Walter B. Martin; William S. Middleton; James E. Paullin; LeRoy H. Sloan; George F. Strong; Chauncey W. Dowden; Paul W. Clough; Major General Norman T. Kirk, Surgeon General, U. S. Army; Capt. Howard H. Montgomery, representing the Surgeon General, U. S. Navy.

By resolution, the Board of Regents dispensed with the reading of the minutes of the preceding meeting but accepted them as published in a recent issue of the *Annals of Internal Medicine*.

The President called upon the Secretary to present communications, which were as follows:

1. A letter enclosing a contribution of \$10,000 from Dr. James D. Bruce, Ann Arbor, Michigan, for the founding of a memorial award to the late Alfred Stengel, "one of the real founders of the College as we know it."

One-half of the award is to be allocated to an annual lecture or award, designating it as the appropriate committee may see fit, to the cause of preventive medicine. Dr. Bruce further specified:

"There are a number of approaches to our educational problems which I shall hope to take up later. One thing that I wish to have understood at this time is that the acceptance of this, or further contributions, involves no obligation on the part of the College to accept any suggestions that I may make. In other words, these contributions are to be used in accordance with the ideals and purposes of the College.

"The magnificent contribution of the College during the war has added to its prestige and further demonstrated the wider rôle it must and eventually will play in medical education. Its policy and activities in this field have been soundly based, and at this time it seems to me that efforts to enlarge these along proved lines would gradually lead to greater usefulness. It has been my hope to assist from time to time with the financial burden, and as a beginning of a fund within the endowment, I should like to make a contribution in the amount of \$10,000, which would permit the establishment of two lectureships or awards. This, together with future amounts which I hope to send from time to time, while kept together as one fund, will be included in the endowment and the income used in accordance with the present policies of the College.

"The policy in the educational field, as I understand it, is to devote these funds to research, scholarships, lectureships, and awards, as well as to the growing responsibility in the postgraduate field."

On motion by Dr. Lee, seconded by Dr. Paullin, it was resolved that the Board of Regents accept this magnificent gift with deep appreciation, and that the President and Secretary General shall confer with the Committee on Fellowships and Awards for the setting up of the Bruce Fund and the setting up of policies and principles regarding its use.

2. A communication from Dr. F. F. Borzell, Chairman of the Wartime Graduate Medical Meetings Committee, in which Dr. Borzell proposed to present to the American College of Physicians office equipment valued at \$288.52, and accompanying his letter was a check for \$397.95, the proportional balance remaining in the treasury from former contributions made by the College.

Dr. Borzell further presented final reports in all detail of the work of the Committee on War-time Graduate Medical Meetings, for filing in the College archives.

A resolution was adopted providing that the report be accepted and filed, and the Board of Regents express to Dr. Borzell and his associates its commendation and appreciation for the magnificent work performed, and also extend its thanks to the committee for the gift of the furniture and equipment and the refund of remaining proportionate fees.

3. A communication from Dr. E. D. Hitchcock, College Governor for Montana, embracing the following resolution adopted at a regional meeting of the College on April 27, 1946, for the combined states of Montana and Wyoming:

"Resolved, that we request the Board of Governors of the American College of Physicians to unite Montana and Wyoming under a single Governorship for purposes of administration.

"Be it further resolved, that this union be continued until such time as Wyoming is able to qualify under a separate state."

After discussion, a resolution by the Board of Regents was adopted authorizing the President to appoint a Governor to serve for both states.

4. A communication from W. C. Mennecke, Secretary, University of Chicago Board of Trustees, acknowledging receipt of \$1,062.40, proceeds from a postgraduate course given for the College at the University of Chicago last autumn, said fund having been used in support of a fellowship in gastroenterology.

This communication was an expression of appreciation for generous assistance from the College.

5. A communication from members of the College in Western Michigan, who on March 20, 1946, at Muskegon, organized a regional group of the American College of Physicians "to promote friendship and understanding among the Fellows and Associates in Western Michigan, and to foster scientific investigation in the field of internal medicine."

6. The next communication was a report prepared by the Executive Secretary, the Educational Director, the Secretary General, the Treasurer, and the Chairman of the Committee on Graduate Courses, as follows:

Program of Postgraduate Courses and the GI Bill of Rights

"The postgraduate courses sponsored by the American College of Physicians are organized primarily for Fellows and Associates of the College. Some non-members may be accommodated when facilities permit, but in the majority of courses, all places are taken by members.

"During the period of World War II, the College charged no tuition fee to any medical officer on active duty or on terminal leave. This courtesy was extended to members and non-members alike. With the termination of the war, and the increased demand for the College courses, our facilities have been taxed to the maximum, with the result that a much smaller number of non-members can be accommodated. In fact, facilities in some courses are inadequate for the member demand.

"The College will be unable to provide veteran medical officers, members or non-members of the College, the benefits of the amended GI Bill of Rights, through which the Veterans Administration would pay tuition fees of medical veterans pursuing its courses. The College has not the administrative machinery to comply with the various and complex regulations through which collections must be made through the Veterans Administration.

"Furthermore, it is believed that the legislators who formulated the original training program for veterans did not have in mind the short one, two or three weeks courses, such as provided by this College. Fees for College courses are comparatively small; all such fees are turned over to the director or institution where a College course is given; the College underwrites all other expenses of promotion, advertising, printing and registration.

"The College regrets its inability, at this time, financially and administratively, to launch upon a program of training for medical veterans, through the Veterans Administration, but will accommodate as many as possible who wish to register in the regular manner."

On resolution unanimously carried, the report was approved.

7. A communication from Dr. Manfred Kraemer of Newark was presented in which the writer decried the use of questions on proposal forms which refer to the candidate's race or religion. The letter was referred to the Credentials Committee after discussion by the Board as a whole.

8. A communication from Dr. Reginald Fitz, Official College Marshal, in which Dr. Fitz desired to retire. The Board of Regents unanimously voted that he should continue this work, especially in view of the fact that it considers no one else so adequately qualified.

9. A communication from Dr. Barnett Greenhouse, F.A.C.P., to Dr. Francis G. Blake, Regent, containing a resolution purporting to correct an embarrassing situation now existing between the American College of Physicians and the American Board of Internal Medicine.

10. A communication from the American Board of Internal Medicine notifying the Board of Regents that certain appointments to the American Board of Internal Medicine will have to be made to fill vacancies which will occur on June 30, 1946.

DR. FITZ: Mr. Chairman, Dr. Waring has been designated Chairman of the American Board of Internal Medicine.

DR. WARING: There are two matters I am instructed to bring to your attention. The first is that the Board would like to increase its membership from nine to twelve

members. This is a necessity because of the very large amount of work to be done, devolving so heavily upon the members of the Board. There should be seven appointees instead of five from the American College of Physicians; five appointees from the Section on Medicine of the American Medical Association, instead of three. We would like to have a panel of names presented and one name will be chosen from that panel to succeed Dr. G. Gill Richards who retires, and two will be added to the list. May I also suggest that when the selection is finally made, notification shall come from the Secretary of the American Board of Internal Medicine.

CHAIRMAN IRONS: I take it that this is largely for the information of the Board of Regents at this time and that it will be acted upon by this Board at its meeting on Friday of this week.

REPORT OF THE SECRETARY GENERAL

DR. GEORGE MORRIS PIERSOL

DR. PIERSOL: The Secretary General wishes to report the deaths of 44 Fellows and 5 Associates since the last meeting of this Board, as follows:

Fellows

Angle, Fred Ernest	Kansas City, Kan.	October 29, 1945
Bartlett, Frank Herbert, Jr.	Muskegon, Mich.	January 25, 1946
Black, Benjamin Warren	Oakland, Calif.	December 1, 1945
Blackford, John Minor	Seattle, Wash.	September 12, 1945
Brasted, Howard Spencer	Hornell, N. Y.	August 28, 1945
Brown, Frederick Lane	New Brunswick, N. J.	January 30, 1946
Brown, Gilbert T.	Dayton, Ohio	November 17, 1945
Carter, Larue D.	Indianapolis, Ind.	January 22, 1946
Evans, Newton	South Pasadena, Calif.	December 19, 1945
Frissell, Lewis Fox	New York, N. Y.	October 24, 1943
Fuller, Frank M.	Keokuk, Iowa	March 19, 1946
Gardner, Edwin Leslie	Minneapolis, Minn.	January 29, 1946
Gober, Olin F.	Temple, Tex.	January 26, 1946
Hallett, Harley James	M.C., U. S. Army	December 11, 1945
Hamman, Louis	Baltimore, Md.	April 28, 1946
Hanes, Frederic Moir	Durham, N. C.	March 25, 1946
Holtzapple, George E.	York, Pa.	February 22, 1946
Hyde, Clarence L.	Akron, Ohio	December 1, 1945
Jennings, Alpheus F.	Detroit, Mich.	November 16, 1945
Jordan, Ferdinand M.	White Plains, N. Y.	August 14, 1945
Kibler, Charles S.	Tucson, Ariz.	February 25, 1946
Lamson, Robert Ward	Los Angeles, Calif.	January 6, 1946
Leathers, Waller S.	Nashville, Tenn.	January 26, 1946
Lowe, Donald Blair	Akron, Ohio	March 2, 1946
Lowry, Tom	Oklahoma City, Okla.	December 11, 1945
Mannheimer, George	New York, N. Y.	December 10, 1945
Manning, Isaac Hall	Chapel Hill, N. C.	February 12, 1946
Matson, Ralph Charles	Portland, Ore.	October 26, 1945
Mercer, Clifford David	West Union, Iowa	December 25, 1945
Mills, Charles W.	Tucson, Ariz.	September 29, 1945
Moore, Alexander B.	Washington, D. C.	March 8, 1946
Palmer, Harold Dean	Philadelphia, Pa.	November 20, 1945

Pierson, Philip Hale	San Francisco, Calif.	January 17, 1946
Ramirez, Maximilian A.	New York, N. Y.	March 4, 1946
Rigney, Lawrence J.	Wilmington, Del.	November 28, 1945
Robertson, Harold E.	Rochester, Minn.	March 8, 1946
Rosamond, Eugene	Memphis, Tenn.	December 12, 1945
Smith, Archibald D.	Garden City, N. Y.	November 22, 1945
Smith, Fred M.	Iowa City, Iowa	February 23, 1946
Stookey, Paul Forrey	Kansas City, Mo.	November 25, 1945
Sturtevant, Mills	New York, N. Y.	October 29, 1945
Trasoff, Abraham	Philadelphia, Pa.	November 24, 1945
Way, Charles T.	Cleveland, Ohio	February 4, 1946
Wright, George Jesse	Pittsburgh, Pa.	October 1, 1945

Associates

Glenn, Paul Mitchell	Cleveland, Ohio	December 21, 1945
Jenny, Thomas Gotthart	Miami, Fla.	August 31, 1945
Jones, Howard	Circleville, Ohio	December 12, 1945
Kugel, Maurice Alexander	Miami Beach, Fla.	March 9, 1946
Marsh, Van Newhall	Talmage, Calif.	July 25, 1945

Since the last meeting of this Board, 88 new Life Members have been added, making a grand total of 488, of whom 40 are deceased, leaving a balance of 448. They are as follows:

Seymour H. Silvers	Brooklyn, N. Y.
Samuel Nesbitt	Arlington, Va.
Elmer E. Glenn	Springfield, Mo.
Wilton Ross Glenney	Pottsville, Pa.
David W. Carter, Jr.	Dallas, Tex.
James F. Slowey	Cleveland, Ohio
Irving Gray	Brooklyn, N. Y.
William M. LeFevre	Muskegon, Mich.
Albert T. Leatherbarrow	Hampton Station, N.B., Can.
Allen H. Bunce	Atlanta, Ga.
Charles T. Stone	Galveston, Tex.
David B. Flavan	St. Louis, Mo.
David W. Kramer	Philadelphia, Pa.
George H. Anderson	Spokane, Wash.
Orange Van Calhoun	Lincoln, Nebr.
W. W. Alexander	Florence, Ala.
Harold W. Gregg	Butte, Mont.
Jacob S. Blumenthal	Minneapolis, Minn.
Frank G. LeFor	Yakima, Wash.
George Tryon Harding, III	Columbus, Ohio
John Francis Briggs	St. Paul, Minn.
Barnet P. Stivelman	New York, N. Y.
Louis L. Perkel	Jersey City, N. J.
Edward James Lynch	Shelton, Conn.
George C. Mackie	Wake Forest, N. C.
Charles H. Harrell	Norfolk, Va.
Harold L. Amoss	Greenwich, Conn.
William G. Gardiner	Toledo, Ohio
Murray Eugene Goodrich	Toledo, Ohio
Francis F. Borzell	Philadelphia, Pa.

Stanley Erwin
 Andrew C. Ivy
 Frank R. Menagh
 Benjamin F. Wolverton
 Harold E. Waxman
 Burton E. Hamilton
 Robert W. Blumenthal
 Henry J. Ullmann
 Frank J. Montrose
 Thomas P. Sharkey
 Clapham P. King
 Joseph Emile Blum, Jr.
 Edmond Michael Walsh
 L. Carl Sanders
 Harry L. Arnold, Jr.
 Edward Saunders Dillon
 Everett C. Jessup
 Frank L. Williman
 John L. Kleinheksel
 Paul D. White
 Daniel L. Sexton
 Henry H. Turner
 Russell S. Boles
 Douglas Deeds
 Titus Holliday Harris
 Ernest L. MacQuiddy
 Treacy H. Duerfeldt
 Paul V. Ledbetter
 Frank R. Mount
 K. W. Benson
 Henry N. Leopold
 Archie Marvin Roberts
 Henry R. Carstens
 J. Sudler Hood
 Eugene Fagan Traut
 Kenneth S. Davis
 Oscar B. Hunter
 James Burnett Shields
 Earl C. Waterbury
 Lorenz W. Frank
 Harold L. Tonkin
 Will S. Horn
 William C. Blake
 Lawrence C. Towne
 William R. Vis
 William C. Nichols
 Henry C. Gotshalk
 Lawrence Arthur Williams
 Virgil G. Presson
 Alfred W. Dubbs
 Gertrude M. Engbring
 Howard Wakefield
 John J. Dumphy

Jacksonville, Fla.
 Chicago, Ill.
 Detroit, Mich.
 Cedar Rapids, Iowa
 Pittsburgh, Pa.
 Boston, Mass.
 Milwaukee, Wis.
 Santa Barbara, Calif.
 Buffalo, N. Y.
 Dayton, Ohio
 Washington, D. C.
 Greenwell Springs, La.
 Omaha, Nebr.
 Memphis, Tenn.
 Honolulu, T. H.
 Philadelphia, Pa.
 Roslyn, N. Y.
 Washington, D. C.
 Wichita, Kan.
 Boston, Mass.
 St. Louis, Mo.
 Oklahoma City, Okla.
 Philadelphia, Pa.
 Denver, Colo.
 Galveston, Tex.
 Omaha, Nebr.
 Tacoma, Wash.
 Houston, Tex.
 Portland, Ore.
 Berkeley, Calif.
 San Antonio, Tex.
 Los Angeles, Calif.
 Philadelphia, Pa.
 Clearwater, Fla.
 Oak Park, Ill.
 Los Angeles, Calif.
 Washington, D. C.
 Glens Falls, N. Y.
 Newburgh, N. Y.
 Denver, Colo.
 Williamsport, Pa.
 Fort Worth, Tex.
 Tampa, Fla.
 Lansing, Mich.
 Grand Rapids, Mich.
 Fargo, N. D.
 Honolulu, T. H.
 Pasadena, Calif.
 Tucson, Ariz.
 Allentown, Pa.
 Chicago, Ill.
 Chicago, Ill.
 Worcester, Mass.

Robert Stanley Flinn
 James J. Waring
 John W. Shuman
 J. W. MacIntosh
 Samuel M. Poindexter

Phoenix, Ariz.
 Denver, Colo.
 Santa Monica, Calif.
 Halifax, N. S., Can.
 Boise, Idaho

CHAIRMAN IRONS: The report of the Secretary General will be received and recorded.

NEW BUSINESS AND REPORTS

DR. PIERSOL: The Committee on Credentials has held two meetings since the last meeting of the Board of Regents—April 14, 1946, and May 12, 1946.

Among communications was one concerning an Advisory Committee in the Brooklyn area to serve with the College Governor for Eastern New York in reviewing candidates. Letters were received from Doctors George E. Anderson, Frank Bethel Cross, Irving J. Sands, and covering letters from Governor Asa L. Lincoln. The Committee on Credentials expressed full agreement and approval of a Brooklyn Advisory Committee. It was the advice of the Committee, however, that there should be no official connection between this Advisory Committee and the Brooklyn Society of Internal Medicine. Governor Lincoln is fully authorized to select an Advisory Committee and to record the names in the executive offices of the College.

Applications for reinstatement to Fellowship.

1. The reinstatement to Fellowship of a former member who is now the dean of an unapproved medical school, against which an injunction is now pending, was not approved by this Committee.

2. Dr. Reuben A. MacBrayer, Fayetteville, North Carolina; his reinstatement is approved by the Credentials Committee with the recommendation that the Board of Regents formally reinstate him on May 12, 1946.

Candidates for Fellowship.

The following is a summary of the recommendations of the Committee (meeting of April 14, 1946):

Recommended for Advancement to Fellowship	35	
Recommended for Election Directly to Fellowship	17	52
Recommended for Election first to Associateship		3*
Deferred		13
Rejected	5	
		<hr/>
		73

Candidates for Associateship.

The following is a summary of the recommendations of the Committee:

Recommended for Election	111	
Fellowship Candidates Recommended for Election first to Associateship		3
Deferred	6	
Rejected	55	
		<hr/>
		172
		*plus 3

A full list of the names of candidates recommended for election to Fellowship and Associateship is included with the list reviewed this morning and later presented in this report for action.

The Committee records that it has recommended that proposals be withdrawn or rejected in numerous cases for the sole reason that said proposals have been on file for more than a year and the candidates, in many cases, have been on military service and have been unable yet to meet all the requirements; consequently, their biographical data become out of date and it is impractical to keep their old proposals on file. The sponsors of such candidates will be notified that this action has been taken without prejudice and that when the candidate is qualified, a new proposal should be submitted.

. . . Formal resolutions were adopted by the Board of Regents approving the recommendations of the Committee on Credentials, reinstating to Fellowship Dr. Reuben A. MacBrayer, Fayetteville, North Carolina, and approving the above report to this point. . . .

DR. PIERSOL (Continuing his report): The second meeting of this Committee was held this morning at 9:30. Several communications were discussed which contained nothing for action by the Regents. One of these inquiries was for the purpose of establishing what standing the College will accord to the "Certificate of Specialization" issued by the Royal College of Physicians of Canada. This is separate and distinct from certification by the Royal College. It does not represent anything comparable to certification, but merely indicates the specialty of the physician. Consequently, the Credentials Committee cannot accept it in lieu of formal certification by an American specialty board or the Royal College of Physicians of Canada.

The following is an analysis of the candidates for Fellowship and Associateship considered by the Committee today:

Candidates for Fellowship.

Recommended for Advancement to Fellowship	15	
Recommended for Election Directly to Fellowship	5	20
Recommended for Election First to Associateship		5*
Deferred		7
Rejected		6
		<hr/>
		38

Candidates for Associateship.

Recommended for Election	85
*Fellowship Candidates Recommended for Election First to Associateship	5
Deferred	19
Rejected	7
	<hr/>
	111
	*plus 5

The Committee on Credentials, therefore, recommends to the Board of Regents the election to Fellowship of 72 candidates and the election to Associateship of 204 candidates.

. . . On resolution formally adopted, the following 72 candidates were elected to Fellowship: (This list was published in the June, 1946, issue of this journal.)

. . . On resolution formally adopted, the following 204 candidates were elected to Associateship: (This list was published in the June, 1946, issue of this journal.)

DR. PIERSOL (Continuing): The following is a report on the candidates elected to Associateship April 20, 1941, five years ago, whose terms now expire:

Already Advanced to Fellowship	65
Deceased	2
Dropped for failure to take up election	0
Rejected previously	1
Rejected today; credentials inadequate (Group A-2)	4
Dropped today; Failed to present credentials (Group B-2)	12
Dropped for Delinquency	0
Resigned	4
Missing in military action (Downs and Stoneburner)	2
Proposals for advancement outstanding (Group A-1)	18
Credentials not presented (Group B-1)	21
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Total Candidates elected, 4/20/41	129

Group A. Proposals for advancement are on file for the following:

1. Military Officers; although these proposals are on file their advancement has been temporarily deferred for additional credentials, but since they are on military service, their time has been extended.

(Group of 18—Names not published)

2. Practicing Physicians; credentials presented but inadequate:

(Group of 4—Names not published.)

Group B. Associates who have not presented adequate (or no) credentials for Fellowship:

1. Military Officers, may have extension of time:

Agnor, Elbert Boogher, Atlanta, Ga. (AUS)
 Burgeson, Paul Arthur, Warsaw, N. Y. (AUS)
 Childs, Edward Patterson, New York, N. Y. (USNR)
 Cummings, Hatch Whitfield, Houston, Tex. (USNR)
 Dickey, Francis George, Baltimore, Md. (AUS)
 Edwards, Robert Allison, Houston, Tex. (AUS)
 Flickinger, Don Davis (MC, USA)
 Green, Mervin Edward, Toledo, Ohio (AUS)
 Hays, James Franklin (MC, USN)
 Kimbrough, Robert Cooke, Jr., Ann Arbor, Mich. (AUS)
 Kwitny, Isadore Jacob, Indianapolis, Ind. (AUS)
 Lynch, George William, Boston, Mass. (USNR)
 Osborne, John Randolph, Middletown, N. Y. (USNR)
 Pritchett, Clark Poston, Columbus, Ohio (AUS)
 Rastetter, Joseph Walter, Milwaukee, Wis. (USNR)
 Reymont, Anthony Edward, Santa Fe, N. M. (USNR)
 Rosenstiel, Henry Carl, Freeport, Ill. (AUS)
 Schneiersen, S. Stanley, New York, N. Y. (USNR)
 Strauss, Arthur Simpson, White Plains, N. Y. (AUS)
 Warr, Otis Sumter, Memphis, Tenn. (AUS)
 Woods, Bertrand Odell, Portland, Ore. (AUS)

2. Practicing Physicians; must now be dropped:

(Group of 12—Names not published.)

Many of these (Group B-2) are very good men but the Committee has no choice if they fail to present their credentials within a period of five years, as specified by the By-laws. All of them have been notified and requested to submit their credentials on several occasions. They are now automatically dropped from the Roster.

. . . On motion, seconded and duly carried, the action of the Credentials Committee was approved and its report approved as a whole. . . .

CHAIRMAN IRONS: Next will be the report of the Committee on Survey, Dr. William S. Middleton, Chairman.

DR. MIDDLETON: Mr. Chairman, the Committee on Survey met on April 14, 1946, and offers the following recommendations relative to changes in the By-laws and regulations. Upon its careful study there were no deviations from the Constitution.

ARTICLE V

Election of Fellows

Section 1. A Fellow of the College shall have met the following qualifications and requirements:

(a) He shall have qualified and served a minimum period of three years as an Associate, except upon recommendation of the Committee on Credentials by reason of very special qualifications as hereinafter set forth.

(b) He shall have graduated from a medical school acceptable to the Board of Regents, at least five years prior to the time of his election, and if engaged in practice, his professional activity must be confined to the field of internal medicine or a related specialty.

(c) If he is not a bona fide teacher or permanent laboratory worker, he shall have been in the actual practice of internal medicine at a permanent location for at least three years preceding nomination for Fellowship.

(d) The criteria of eligibility for election to Fellowship are bi-lateral:

1. Detailed information concerning the candidate's hospital and academic appointments, with particular reference to the size and nature of the hospital service and the exact teaching responsibility; published contributions in media acceptable to the Committee on Credentials, with particular emphasis upon papers published during the period of Associateship; personal approval by Fellows in his territory, with reference to his character, ethical standing and medical activities; evidence of postgraduate training and attendance upon the Annual Meetings of the College.

2. He shall be certified by the recognized national board of certification in his particular field, where such an accrediting board exists. This regulation, however, shall not apply to candidates who were elected to Associateship prior to April 6, 1940, nor to candidates from the Army, Navy and Public Health Services who were elected prior to and including April 1, 1944.

PROPOSAL

Section 2. His name shall be proposed in writing by a Master or Fellow of the College from the same state, province, or territory, not an officer or member of the Board of Regents; he shall be seconded by another Master or Fellow from the same state, province or territory and endorsed by the member of the Board of Governors

from the state, province or territory in which he resides, or by the Surgeon General of the Army, Navy or Public Health Service of which he is a member, or by an Officer of the College or by a member of the Board of Regents. His nomination must be accompanied by a written statement made both by the proposer and the seconder, containing all of the above cited qualifications of the candidate. Further, the name of the candidate shall be sent to each Fellow in the candidate's locality with the request for comments as to the candidate's fitness. The proposer must be prepared, moreover, to add such further information as may be requested by the Committee on Credentials.

Successful candidates shall be so notified immediately after their election and shall be urged to attend the next succeeding Convocation, when Fellowships will be formally conferred. The official Fellowship Certificate, signed by the President and the Secretary General, shall be issued following the Convocation. Acknowledgment of its receipt shall be made upon an official card, signed and dated by the newly elected Fellow, and returned to the Executive Secretary, to be added to the official College roll.

Section 3. Proposals for direct election to Fellowship, with or without prior certification by the appropriate certifying board, may be made to the Committee on Credentials. This manner of election is an unusual mark of distinction; hence such candidates must be preëminent in teaching, research or clinical practice. In advancing individuals for such consideration, the following details must be furthermore considered: maturity, national reputation, publications and other contributions to medical science and public welfare. It is obvious that the Committee on Credentials will exercise due discrimination in all proposals for direct election to Fellowship. For this reason, complete data concerning the candidate and his activities must accompany the proposal.

This ruling will not be invoked for candidates who have failed of regular advancement from Associateship to Fellowship.

ARTICLE VI

(new article)

Election of Masters

Section 1. A special committee on Masterships will be named by the President. This committee will consist of two members from the Board of Regents and one member from the Board of Governors. It will bring its nominations of Masters to the Board of Regents for election.

ARTICLE VII

(Replacing Article VI)

Section 1. An Associate of the College shall have met the following qualifications and requirements:

(a) He shall hold the degree of M.D., M.B., or M.D., C.M., from a medical school acceptable to the Board of Regents.

(b) If engaged in the practice of medicine, the candidate, after receiving his degree, shall have had at least one year of internship in an approved hospital and three years of graduate training in internal medicine or allied fields. One year of this graduate training may be spent in the basic sciences. By an alternative plan, instead of an organized system of graduate training such as is afforded by a residency or fellowship, a candidate may satisfy this requirement under the preceptorship

of a recognized specialist approved by the American Board of Internal Medicine or a similar certifying Board, after conference with the Committee on Credentials. Such opportunities must be approved by the American College of Physicians prior to their acceptance in lieu of the conventional graduate training. Under no circumstances can this plan be made retroactive.

(c) He shall be a member in good standing in his local, state, provincial or territorial and national medical societies, except in the case of those not engaged in practice, such as full-time teachers, research workers, those holding official hospital positions, etc.

(d) If a practitioner, he shall be licensed to practice medicine in his state, province or territory, and shall indicate his purpose to practice internal medicine from the date of his application, or be a Medical Officer in the Government Service, either in the United States or the Dominion of Canada, in American or Foreign Service. If not a practitioner, he shall hold an official institutional position in one of the allied branches of internal medicine or in medical research.

PROPOSAL

Section 2. His name shall be proposed on the official blank of the College by a Master or Fellow residing in the same state, province or territory, not an Officer or member of the Board of Regents; he shall be seconded by another Master or Fellow also from the same state, province or territory, and endorsed by the member of the Board of Governors from the state, province or territory in which he resides, or by the Surgeon General of the Army, Navy or Public Health Service, of which he is a member, or in special instances, by an Officer of the College or by a member of the Board of Regents.

The credentials of candidates for Associateship shall be considered first by the Committee on Credentials, which Committee shall report to the Board of Regents for election or rejection.

Successful candidates shall receive at once, from the Board of Regents through the Executive Secretary, an appropriate official notification of their election to Associateship in the College.

TERM OF ASSOCIATESHIP AND ELIGIBILITY FOR FELLOWSHIP

Section 3. Candidates so elected shall be continued as Associates for a term not to exceed five years.

Such Associates shall be eligible for election to Fellowship at the end of three years after election to Associateship. Upon expiration of this three year period he shall be notified in writing by the Committee on Credentials of his eligibility for election to Fellowship during the next two years, provided he shall have met within that time the requirements necessary for Fellowship. If not elected to Fellowship within five years, his Associateship automatically ceases.

CHAIRMAN IRONS: Perhaps Dr. Middleton will explain to us in what respects this makes changes in the present By-laws.

DR. MIDDLETON: The present By-laws are modified in only a few respects. The Committee was charged with the responsibility of clarifying the circumstances of certification by the American Board of Internal Medicine. There had been a general disapproval among the Board of Governors relative to certification being a prerequisite for admission to Associateship. That position was sustained unanimously by the Survey Committee. It felt that while it is a great step in the evolution of the training of a man for Fellowship, certification should not be a barrier to his entrance upon the responsibilities of Associateship, which in a sense is merely a probationary term before the candidate advances to the maturity of Fellowship.

The proper implementation of the preceptorship into a system whereby the American College of Physicians could participate with the American Board of Internal Medicine in the recognition of exposures other than ordinary residencies and fellowships might be a very important link. It was suggested by Dr. Meakins in the American Board of Internal Medicine that these preceptorships offer to many young men opportunities that are at least as good as the educational outlet of a residency; accordingly, it was deemed wise that the American College of Physicians enter into a reciprocal relation with the American Board of Internal Medicine in recognizing preceptorship as a stage in development.

If we are going to hold to the standards of admission to Fellowship, there should not be erected between the College and the American Board—one a rating group and the other a qualifying group for Fellowship—such a barrier that it cannot be surmounted by an individual who answers one and yet, because of the strictures of the other, is forbidden Fellowship in the American College of Physicians.

In effect, there are only two major changes—one having to do with the requirement of certification by the American Board of Internal Medicine, or a similar certifying Board, for advancement to Fellowship, rather than to the earlier suggestion of certification as a prerequisite for Associateship; and the second, the preceptorial plan as implementing training for the men who perhaps prefer the preceptorial plan to a residency or fellowship. The small third item of change is purely a geographic one—meaning that a candidate's sponsors shall come from the same state, province or territory in which the candidate resides.

: I believe provision should also be made for candidates from Mexico and Central American States. While it has been customary to accept candidates from any part of North America or any of its dependencies, there is nothing in the Constitution that admits it.

DR. MEAKINS: I should think that Newfoundland, Greenland and even Iceland would be included also in North America. The Committee will want to consider all the geographic possibilities.

DR. DOWDEN: Mr. Chairman, I understand a candidate is not eligible for Associateship until three years after he has graduated. Then there is a five year period of Associateship during which he must qualify for Fellowship, although he may present his credentials in three years. There are at least six years after graduation before he is eligible to take the examinations of his specialty Board. Consequently, the date of his eligibility for Fellowship and his eligibility to take the Board examinations is the same—two periods of three years each. Is that correct, Dr. Middleton?

DR. MIDDLETON: Exactly. In other words, he cannot take the Board of Internal Medicine examinations until five years after his first year of internship.

DR. LEE: Mr. President, I am going to suggest that this ought to be referred to the Board of Governors because that Board is a little bit closer to the incoming Associates and Fellows and I think before we pass upon this matter, it should be referred to the Board of Governors for their comments; therefore, I move that this be referred to the Board of Governors for any comments that they may make and that it then be returned to this Board for action, but no action be taken at this time.

. . . The motion was seconded by Dr. Stroud and carried. . . .

DR. WARING: I should like to discuss the matter of preceptorships in the American Board of Internal Medicine. Last night the Board had a very thorough discussion upon this matter especially with regard to the difficulty of passing judgment and approval upon men applying as preceptors. We came to the conclusion that because of these difficulties it would be wise to do away entirely with preceptorships and the unanimous decision was that as of July 1, 1947, all preceptorships shall end. Between now and then the Board will take no new preceptors.

DR. MIDDLETON: I am very sorry to hear this. I believe it to be a backward step, if I may say so. I dislike to see the time pass when eminent teachers and clinicians may have in their offices young men coming into the field of internal medicine by reason of exposures that are highly advantageous from an educational standpoint. I agree, the difficulties of control are obvious. The Board had an earlier expedient to tell just how good these exposures proved to be by the result of particular training. A candidate or two from a preceptor in a community in which the Board was in doubt, would very shortly reflect the adequacy or inadequacy of his training when he came up for examination. I believe there are two particular ends, educationally, that we are meeting here. First, the end of the men who need training; the inability of our educational institutions; the other end of a type of probationship that the man goes through as a house fellow after the earlier period, living in the very atmosphere of medicine, whether it is the hurly-burly daily practice, or the office or the clinic, that cannot possibly be replaced by the large organized educational program of a general hospital.

DR. WARING: It has seemed to members of the American Board of Internal Medicine that preceptorship is becoming a matter whereby a young man goes into an older doctor's office, does much of his hack work for him, makes his night calls and some of his other less attractive calls and there is little actual definite supervision of his work. It is for that reason that the Board decided that the preceptorship plan is difficult of appraisal in the first place, and the number of applications as preceptors has increased very greatly.

CHAIRMAN IRONS: The Chairman is fully in accord with Dr. Middleton. We shall bow to the feeling of the Board. There simply are not the opportunities available in this country for all of the men who want this kind of training. I agree, it is tremendously difficult to evaluate these preceptorships, but just the same, it does seem that men with proper preceptors can get much valuable training.

DR. BARR: Does this action of the Board of Internal Medicine mean that it will not accept training by men they think can give training, or that the Board has ceased to recognize officially and permanently a certain list of preceptors?

DR. WARING: The American Board has a list of 25 or 30 preceptors recognized to date; any young men working under these are approved, after a certain number of years, as meeting certain requirements of the Board. The American Board has carefully reviewed its list of preceptors; certain of them do not meet the requirements fairly; the Board knows from personal experience that the training being given to some of the young men under some of these preceptors is inadequate from the Board's standpoint. Because of the great difficulty in passing on all the additional applications of preceptors and because of certain inadequacies among the present list, the Board decided that the present preceptors shall function until July 1, 1947; that in the interval the Board will recognize no other preceptors; that after July 1, 1947, there will be no further recognized preceptors. I agree with the Chairman that there are many men that could meet these requirements, but the difficulty of being sure about them, the difficulty of refusing one or another doctor as a preceptor seems almost insurmountable.

DR. MEAKINS: Mr. Chairman, in speaking of this matter I think we have to be realistic as to where these men are going to obtain three years of residency in hospitals in North America. They may obtain it at a teaching hospital but there are very few who after their junior internships can go on for three years. The openings just don't exist in a teaching hospital. If it is in a non-teaching hospital, what guarantee has the American Board of Internal Medicine that just three years in any hospital is going to be efficient training? There are hospitals and hospitals. In some of them the training is bad and it should never be accepted. Furthermore, some years ago we visualized that a man might go to Europe and take his training

there. This, of course, has not been possible for the last few years. Now, to make up for this gap, which I think is a very real gap, a good resident training in the hospitals of North America, we visualize the possibility of a few men taking these young candidates, not as slaves, not as night workers, but for real training. I don't think the list of preceptors should be 42; I would reduce that by half.

CAPT. MONTGOMERY: Referring back to the proposed requirements for membership in the College, I invite attention to the wording of Section 1 (c): "If he is not a bona fide teacher or permanent laboratory worker, he shall have been in the actual practice of internal medicine at a permanent location for at least three years preceding nomination for Fellowship."

A strict reading of this might make it extremely difficult for any medical service officer. For instance, his residence is not permanent and is not of his own selection and the three years, if considered consecutive preceding nomination, might render his eligibility impossible.

DR. MIDDLETON: The Credentials Committee has not interpreted this regulation strictly in the past with regard to medical officers, for many from the Services have qualified. A correction might readily be included, however.

DR. MARTIN: How about the Veterans Bureau being included in those changes?

CHAIRMAN IRONS: That, too, should go in.

May we now have the report from the Committee on Fellowships and Awards. Dr. Francis Blake.

DR. BLAKE: The Committee on Awards received during the year 178 inquiries with respect to Clinical Fellowships. Of these, 51 bona fide applications were filed. Of these, five were withdrawn before Committee action. A preliminary screening reduced the number from 46 to 30 qualified applicants. Thirty were circulated to the Committee. Ten have been appointed as follows:

Dr. Joseph M. Barker, cardiology at the University of Michigan, from January 9, 1946—\$3,000.00.

Norman L. Cressy, infectious diseases at Yale University, from February 1, 1946—\$3,000.00.

John Franklin, internal medicine at Johns Hopkins Hospital, upon release from military service—\$2,400.00.

John B. Hickam, circulation at Emory University, from June 1946—\$2,500.00.

John S. Hunt, infectious diseases at Vanderbilt University, from April 1, 1946—\$2,000.00.

Albert W. Lapin, Montreal, cardiology at the University of Michigan, Emory University, and Massachusetts General Hospital, from May 1, 1946—\$1,800.00.

Gordon S. Myers, cardiology at Massachusetts General Hospital, from October 1, 1946—\$2,400.00.

E. A. Rasberry, Jr., gastro-enterology at University of Pennsylvania, from July 1, 1946—\$2,400.00.

Hugh Tatlock, clinical medicine at Yale University, from September 1, 1946—\$3,000.00.

Philip A. Tumulty, internal medicine at Johns Hopkins Hospital, from January 1, 1946—\$2,500.00.

That completes the appointment of Clinical Fellows and uses the \$25,000 appropriated by the College for this purpose.

There have been 11 applications for Research Fellowships. One appointment was made at the December meeting, of Kenneth A. Evelyn, Montreal, to work with Dr. J. C. Meakins and Dr. C. Lyman Duff at the Royal Victoria Hospital. It is now recommended that two other candidates be awarded Research Fellowships by the College. The first of these is Charles P. Emerson, Jr., of Boston. He was

awarded a Research Fellowship just prior to the war but withdrew from it to enter the Army. He has now re-applied. He proposes to work at the Thorndike Memorial, Boston City Hospital, under the direction of Dr. George R. Minot and Dr. William B. Castle, from June 1, 1946—\$2,500.00.

The second recommendation is that a Fellowship be awarded in research to Dr. Thomas S. Sappington, of New Haven, Connecticut. He is a graduate of Harvard Medical School, 1941. He has since that time had training at Yale and at the New Haven Hospital. He desires to work on nitrogen metabolism in the field of gastrointestinal disease under the direction of Dr. H. L. Bockus at the Graduate Hospital of the University of Pennsylvania, Philadelphia, from October 1, 1946—\$2,500.00.

That makes three Research Fellows at a stipend of \$2,500.00 each, using \$7,500 appropriated by the College for this purpose.

I would move approval of the recommendation of the Fellowship Committee for the appointment of Drs. Emerson and Sappington as Research Fellows. I also move approval of the appointment of the Clinical Fellows as read.

. . . The motion was seconded by Dr. Middleton and carried. . . .

CHAIRMAN IRONS: The next will be the report of the American Board of Internal Medicine, Dr. Reginald Fitz, Chairman.

DR. FITZ: We have had a successful year and have just completed examining a group of more than 200 men. The work of the Board has been carried on about the same as usual. We are facing practically a renovation of the Board at the beginning of the next fiscal year, July 1. You have already learned of the desirability of increasing the size of the Board. As far as we can determine from our Constitution, it is within the power of the Board to increase its membership. We obtained legal advice on that point. We would like to have seven members from the College and five members from the Section on Medicine of the American Medical Association. We understand that the Board of Regents of the College will make nominations at its meeting on Friday of this week and the Board of Internal Medicine will thereafter make the elections. The financial status of the Board is satisfactory.

CHAIRMAN IRONS: This report will be received. Dr. Clough, our Acting Editor, will kindly report.

DR. CLOUGH: As yet there has not been a meeting of the Committee on the ANNALS. I have very little that is new. So far as material is concerned, we are getting a larger number of articles submitted. Many of them are still not too good; probably less than half of those that have been submitted are accepted. Material to fill the June, July and part of the August issues has already gone to the printers and in addition we have twenty main articles accepted for publication and about ten more under consideration which are likely to be accepted. This would run us for a full three months period beyond August. That is about as large a backlog of articles as it is desirable to have under present conditions, because if we postpone publication too long, we get the reputation of holding up articles until they are stale. We have tried to give priority to certain articles that seem to be of current interest and importance.

We have an ample number of case reports for publication. Now that we have resumed the Annual Meetings, and shall obtain manuscripts of the papers there, we shall have an abundance of material from which to select.

In accordance with the advice of the Board of Regents, we did not accept the proposition to publish another number devoted wholly to medical-legal articles, but we have accepted about five individual articles, scattering them one at a time.

So far as promptness of publication is concerned, we have done as well as we could, with the exception of the Convention number which was held up for several days to get the complete program. Our manuscript material has been on time. There is still, however, substantial delay in printing so that most of the numbers have not appeared until very late in the month. I do not think there is anything that the

editor's office can do about that. Editorials, I think, are the most difficult problems there are to handle; if any members of the Board of Regents have ideas which they would like to incorporate in editorial form, they would be most welcome. We have not been able to get out book reviews satisfactorily as yet, but I think from now on there will be enough available men capable of reviewing a book to enable us to get out a reasonably large number. The only other thing that I planned to recommend to the Committee on the ANNALS relates to the salary of one of our secretaries who asked for a substantial increase. After consulting with the Executive Secretary of the College, we granted her temporarily an increase from \$1440.00 per annum to \$1800.00 per annum. I should recommend through the proper channels that eventually this be made permanent.

•**SECRETARY LOVELAND:** The last matter has been placed on the agenda of the Finance Committee. The recommendation was absolutely necessary to keep Dr. Clough's work from being seriously interrupted.

Supplementing Dr. Clough's report, we are having far greater difficulties in getting adequate paper now than during the war. The printers have greater difficulty with labor in getting the ANNALS printed. It isn't the fault of the Acting Editor or of the printers; but the fault of current postwar conditions. We think we have one of the best printing establishments in the country but they are experiencing many difficulties.

We are experiencing difficulty in determining the quantity of the ANNALS to print. With the termination of the war and the eventual cancellation of Army and Navy orders for the ANNALS, we anticipated a slump in circulation. Quite the opposite is our experience. Subscriptions keep pouring in in unexpected numbers with the result that stock of past issues is promptly exhausted. From month to month we have been increasing the order to our printers, but with the shortage of paper, we naturally do not want large overruns. We believe by July the situation will be reasonably leveled so that we can more accurately estimate in advance the quantity required.

DR. CLOUGH: I believe Dr. Pincoffs will be able to resume the editorship within the relatively near future. It is only recently that he has been technically discharged from the Army.

CHAIRMAN IRONS: The ANNALS have profited under your able editorship very much, Dr. Clough, and we thank you.

Reports from other committees will be received at the next meeting of the Board of Regents.

. . . The Secretary read various announcements and the meeting was adjourned at 4:45 p.m. . . .

Attest: E. R. LOVELAND,
Executive Secretary

MAY 14, 1946

The second meeting of the Board of Regents during the Philadelphia Annual Session was held at Convention Hall, Tuesday, May 14, 1946, at 12 o'clock noon, with President Ernest E. Irons presiding, Mr. E. R. Loveland acting as Secretary, and with the following in attendance:

Drs. David P. Barr; James J. Waring; William D. Stroud; George Morris Piersol; T. Homer Coffen; Jonathan C. Meakins; Hugh J. Morgan; Francis G. Blake; James F. Churchill; Reginald Fitz; Roger I. Lee; Charles T. Stone; Walter B. Martin; James E. Paullin; LeRoy H. Sloan; George F. Strong; Paul W. Clough; Chauncey W. Dowden; C. C. Shaw, Educational Director; and, in addition, Rear Admiral George W. Calver (MC), USN, and Dr. William J. Kerr, a former President of the College, were present as guests.

The meeting was called to order by President Irons, the Secretary recorded the roll and presented a transcript of the minutes of the preceding meeting of the Board which, by common agreement, were not read in toto.

CHAIRMAN IRONS: Some weeks ago, Admiral Calver, of Washington, wrote asking to be allowed to present certain facts which he and his colleagues have developed with respect to the changes in the medical set-up in this country. Admiral Calver has brought with him certain documents and while I am sure we shall not have enough time to go into them very extensively, we shall be glad to listen to him in a brief discussion of the program, administratively.

. . . Admiral Calver presented, at some length and with appropriate discussion, various bills including S. 2143 and H.R. 3293 pending before the 79th Congress in the House of Representatives and the Senate of the United States, dealing with health service plans. His remarks and the plans and proposals were, by request, removed from the record. . . .

CHAIRMAN IRONS: Our first official report will be from the Board of Governors, Dr. Dowden, Chairman.

DR. DOWDEN: First of all, I want to refer to combined meetings of the Regents and Governors. One of the last things my predecessor, Dr. William Breed, did before he passed on, was to send a letter to each member of the Board of Governors asking for his reaction to the combined Regents and Governors meeting held therebefore in Chicago. I was much interested in the reports from the Board of Governors and the enthusiasm with which the various Governors answered that letter, and how anxious they were to have those meetings continued.

Dr. Edward L. Bortz has been elected Vice Chairman of the Board of Governors, that office having been vacant since I became Chairman automatically following the death of Dr. Breed.

The report from the Survey Committee was read by Dr. Lathrope, but the hour was drawing late, everyone was tired and it seemed very evident the report would be very far-reaching and that extemporaneous discussion would get us nowhere, so it was suggested that mimeographed copies of the report be sent to every Governor for study and then be discussed at the next meeting of the Board of Governors the following year before any report by the Governors can be made to the Board of Regents.

It was suggested that it would require two years at least to make the necessary changes if we waited a year to discuss it and another year to allow for the change. The motion finally put was that these reports be mimeographed and sent to each Governor and they should make their own comments after studying it thoroughly and send them to the Chairman who in turn would report to the Regents at its autumn 1946 meeting. There are two objections to that, as I see it. Much will be said by each Governor, but it is going to be rather difficult to crystallize and consolidate their opinions. It would be rather simple if we could have the whole discussion together and arrive at some common opinion. I, therefore, doubt if my report to you in the autumn will have great value. I hope the Board of Regents will not act upon this very important resolution until we have a chance for a combined meeting of the Governors and Regents. This matter is entirely too important to pass upon without a very careful study. It has to do with the future of the College and it deserves a great deal of thought and deliberation.

I have received numerous letters from time to time from members of the Board of Governors, but I am not going to take much of your time now for discussion. However, here is a short letter from Dr. Moffatt, of Montreal, who says, "There appears to be a considerable percentage of rejections for admission to Associateship. Do you not believe that if some grounds upon which these rejections are made are

better known to the Governors, without entering into personalities, that it would serve as a guide in selecting candidates?" Such matters are intimately connected with other things which should be discussed; they are intimately associated with this discussion of the proposals by the Survey Committee.

. . . On motion by Dr. Paullin, seconded by Dr. Fitz, and carried, it was RESOLVED that action on the report of the Survey Committee be deferred until after the Regents and Governors have received mimeographed copies thereof. There followed discussion of the possibility of having a joint meeting of the Governors and Regents during the current week and it was determined to have the report of the Survey Committee mimeographed immediately and to arrange a joint meeting of the Regents and Governors on Wednesday, May 15, at 12 o'clock noon. The Chairman of the Board of Governors, Dr. Dowden, pointed out that even by having a joint meeting on such short notice, it probably would not be feasible to take final action on such short notice, but that common discussion would clarify many points. . . .

CHAIRMAN IRONS: May we have the report of the Committee on Constitution and By-laws, Dr. Paullin, Chairman.

DR. PAULLIN: Mr. Chairman, the Committee on Constitution and By-laws offers an amendment to the By-laws, Article 4, Section 2, as an added paragraph:

"The members of the Board of Governors shall each serve for a term of three years and not more than two consecutive terms." From the minutes of the Board of Regents, the Committee was directed to prepare a proper By-law for the above and this amendment would be presented for adoption at the next Annual Business Meeting of the College. I move the adoption of this amendment.

DR. PIERSOL: I second the motion.

MEMBER: I am all for the change. The more we rotate the officers, the more men we will get into the fold.

MEMBER: Could a Governor be returned to the Board again later after serving two consecutive terms?

CHAIRMAN IRONS: A member could be off for awhile and then be returned to the Board.

MEMBER: Has the Board of Governors been asked about this? What is their reaction?

DR. DOWDEN: It was up for brief discussion yesterday, but it is particularly scheduled for discussion tomorrow. Thus far most of the sound thinkers on the Board have been very much opposed to this resolution. In the first place, it is believed that the men who have attained the greatest prominence as well as the greatest usefulness in and to the College, have come up by way of the Board of Governors. I could name a great many of them, but you know them yourselves; practically all of them were Governors for more than six years. Probably many of these men would have been ineligible for the higher offices at the end of the six year term, for they were just then reaching their period of greatest usefulness and influence. I do not think the term of Governors should be over 9 years, or 3 consecutive terms. I feel that you are penalizing the College, and while you will be getting rid of some of the older men, you are going to sacrifice some young men who are coming on a little later and who are going to be of great help to the College.

. . . There followed some general discussion in which members of the Board of Regents participated generally. There were some who felt that the new proposal should not be rushed through too quickly and others who felt that the recommendations should be modified to provide for a maximum of three consecutive terms of three years each. Furthermore, it was pointed out that if this By-law were adopted,

the Nominating Committee would have to revise its slate of nominations for Governors and that there would not be adequate time to do this in the midst of the General Business Meeting. It was also pointed out that the Board of Regents had originally been responsible for adopting a self-denying ordinance itself, limiting the terms of the Regents to two consecutive terms. Many thought that theoretically some limitation should be adopted to end criticism of the College being directed "by the same old crowd", and that younger men ought to be given an opportunity. On motion by a member, seconded and regularly carried, it was resolved that this resolution for the adoption of an amendment to the By-Laws, limiting tenure of Governors to two consecutive terms, be laid on the table. . . .

CHAIRMAN IRONS: Next we have the report of the Advisory Committee on Postgraduate Courses. Dr. Bortz, the Chairman, is not present, nor is the Educational Director, Dr. C. C. Shaw, and we are asking the Secretary, Mr. Loveland, to give a report in brief.

SECRETARY LOVELAND: Dr. Shaw had prepared a detailed report about the initiation of a program for the aid of veterans, the conferring of Fellowships and the conduct of our postgraduate course program. A part of this has already been covered by the report of Dr. Blake, Chairman of the Committee on Fellowships and Awards. In regard to our postgraduate courses, ten have been organized on our spring schedule and practically all of them have been over-subscribed. An outline of the courses is as follows:

No.	Dates	Title	Director	Institution
1	(three sections) A—March 4-9 B—April 8-13 C—July 8-13	Clinical Allergy	F. M. Rackemann	Mass. Gen. Hosp.
2	March 18-23	General Medicine	H. A. Reimann	Jefferson Medical College
3	March 25-30	General Medicine	Charles T. Stone	Univ. of Texas School of Medicine
4	April 1-19	Internal Medicine	James H. Means	Mass. Gen. Hosp.
5	June 3-8	Metabolism and Nutrition	Tom D. Spies	Hillman Hospital
6	April 22-27	General Medicine	James E. Paullin	Emory University School of Medicine
7	April 29-May 4	Gastro-enterology	Henry L. Bockus	Graduate Hospital
8	May 6-11	Cardiology	Wm. G. Leaman, Jr.	Woman's Medical College of Pa. and Philadelphia General Hospital
9	May 6-11	Thoracic Diseases	John Alexander	University of Michigan Medical School
10	June 17-28	Internal Medicine	Stacy R. Mettier	University of California

The majority of the registrants have been members of the College. A fair proportion, possibly one-third, were medical officers in the Armed Services or returning veterans. A comparatively small number of non-members could be accommodated because of limited facilities.

A program of 17 courses has been prepared for the autumn of 1946, but, due to

certain extenuating circumstances, the number will be reduced to 13, for which the schedule is as follows:

No.	Dates	Title	Director	Location
1	Sept. 2-14	Internal Medicine	R. R. Snowden	Pittsburgh, Pa.
2	Sept. 23-28	Psychosomatic Medicine	Franklin G. Ebaugh	Denver, Colo.
3	Oct. 7-19	Internal Medicine	Homer P. Rush	Portland, Ore.
4	Oct. 14-18	Clinical Neurology	Bernard Alpers	Philadelphia, Pa.
5	Oct. 21-26	Hematology	Charles A. Doan	Columbus, Ohio
6	Oct. 21 to Nov. 1	Internal Medicine	Wallace M. Yater	Washington, D. C.
7	Nov. 4-9	Allergy	Robert A. Cooke	New York, N. Y.
8	Nov. 4-9	Cardiology	Paul D. White	Boston, Mass.
9	Nov. 11-16	Gastro-enterology	Walter L. Palmer	Chicago, Ill.
10	Nov. 18-23	Internal Medicine	Joseph M. Hay- man, Jr.	Cleveland, Ohio
11	Nov. 25 to Dec. 6	Internal Medicine	J. C. Meakins	Montreal, Que.
12	Dec. 2-7	Chemotherapy	W. Barry Wood, Jr.	St. Louis, Mo.
13	Dec. 2-7	Cardiology	Frank Wilson	Ann Arbor, Mich.

It is the purpose of the Advisory Committee on Postgraduate Courses to make these courses more substantial and fundamental, to limit the number of very short courses and to increase the number of courses of two, three or four weeks.

A matter that needs the approval of the Board of Regents is that of the fees charged for small clinical courses where the registration is very limited. This spring we had a series of three courses on clinical allergy, each limited to six registrants. Obviously, our own rates of tuition fees of \$20.00 a week to members and \$40.00 a week to non-members are totally inadequate for these small courses. The Committee on Postgraduate Courses and the Committee on Finance have been consulted and they are in agreement that we recommend to the Board of Regents that the tuition fees be increased to \$40.00 and \$80.00 for members and non-members, respectively, in the case of purely clinical courses where the registration is limited to 12 or less. One member of the Committee who approved it said he did so reluctantly and, therefore, it is felt that the Board of Regents should officially pass on this matter as a principle.

. . . A motion was made, seconded and regularly carried, approving the recommendation with regard to fees for restricted clinical courses with registration limited to 12 or less. . . .

SECRETARY LOVELAND: Another matter in connection with the postgraduate courses of the College is that Dr. C. C. Shaw, who has served as Educational Director since November 1, 1945, has tendered his resignation as of May 31, 1946, to accept another appointment. His resignation has already been accepted by the Executive Committee of the College, and the Secretary General, the President and the Executive Secretary were authorized to appoint a successor, not as Educational Director but as an Executive Assistant to the Executive Secretary. A number of candidates have been interviewed and we are ready to recommend the appointment of Mr. Frederick Pindar to this post on June 1, but he will be unable to devote his whole time to the College until September 1. Mr. Pindar has been thoroughly investigated. He has a fine record of training and experience, his most recent work being, for the past four or five years, the Assistant to Dr. A. N. Richards, Vice President of Medical Affairs of the University of Pennsylvania. Recommendations of the most acceptable type have been received from many men whom you will know, such as Dr. Richards, himself, Dr. O. H. Perry Pepper, and various administrative officers of the University and others.

. . . On motion, seconded and regularly carried, the action by the President, Secretary General and Executive Secretary in appointing Mr. Pindar was approved.

CHAIRMAN IRONS: Is there a report from the Committee on Educational Policy, Dr. Lee, Chairman?

DR. LEE: The Committee has no formal report. I sat in at the meeting of the Advisory Committee on Postgraduate Courses; the discussion was purely general and it was recognized that the immediate conditions were very transient.

CHAIRMAN IRONS: May we have a further report from the Committee on Credentials now?

DR. PIERSOL: The Committee on Credentials held a special meeting yesterday at which all members were present. The Committee believes that it is necessary, in order to safeguard properly the interests of the College, that the present proposal form for admission be retained, amplified and changed as occasion arises to meet contemplated new requirements.

DR. DOWDEN: I move the report be adopted.

DR. PAULLIN: I second the motion.

CHAIRMAN IRONS: The matter is open for discussion. The Chairman would like to see this matter very carefully considered to avoid unfavorable discussion and the development of prejudice among people who do not understand the origin of the American College of Physicians.

. . . There followed general discussion with practically every member of the Board participating, many feeling that the advice and experience of the Credentials Committee should be followed, and an equal number recommending that questions on the proposal blank referring to race and religion be deleted. . . .

CHAIRMAN IRONS: May we have the report of the Committee on Public Relations, Dr. Lee, Chairman?

DR. LEE: The Committee on Public Relations met this morning. It recommends the adoption of the following resolution, which I move:

RESOLVED, that the Fellowship dues of Dr. Henry I. Shahon, Roxbury, Massachusetts, and Dr. Jacob Jesse Singer, Beverly Hills, California, be waived for 1946 and until their resumption of practice, this action due to present illness.

. . . The motion was seconded and passed. . . .

DR. LEE (Continuing): The Committee received two resignations and recommends the following:

RESOLVED, that the resignation of Dr. Newton Thomas Saxl, F.A.C.P., New York, New York, be accepted.

RESOLVED, that instead of accepting the resignation of Dr. John A. Wentworth, F.A.C.P., Hartford, Connecticut, he be retained on the Roster and his dues waived because of ill health, the waiver to continue until his recovery and resumption of work.

. . . Both motions were seconded and unanimously passed. . . .

. . . Dr. Lee, continuing his report, presented a disciplinary case, that of an Associate of the College against whom charges had been received, including conviction by the Federal Government as a result of income tax evasion and other unprofessional conduct. After careful review and discussion, a resolution was adopted, providing that formal charges be instituted and action be taken in accordance with provisions of the By-laws of the College. . . .

DR. LEE (Continuing the report of the Committee on Public Relations): The next item in our report refers to members to be dropped for delinquency in dues of two or more years time. Dr. _____, F.A.C.P., Ukiah, California, is delinquent since January 1, 1944, and answers no communications. Dr. _____, Woodhaven, New York, is likewise delinquent for more than two years.

The provisions of the By-laws make it incumbent upon the College to drop these two members from the Roster and the Committee recommends that their names be so dropped and I so move.

. . . The motion was seconded and carried. . . .

DR. LEE (Continuing): The Committee has a communication from Dr. Ernest C. Faust, Secretary of the American Academy of Tropical Medicine, requesting that the American College of Physicians join with various other organizations in sponsoring a meeting in 1947, or as soon as practicable, on the general subject of Tropical Medicine, and that the President of the College be empowered to appoint a member or representative. There will be no financial obligation. The proposed resolution is a long one, but the Committee can see no objections to it. The resolution is as follows:

"BE IT RESOLVED, that the American College of Physicians heartily endorse the proposal of the American Academy of Tropical Medicine that an international congress on tropical medicine and malaria be held in the United States at an early date, and that the American College of Physicians join with the American Academy of Tropical Medicine, in petitioning the State Department of the United States government to sponsor officially, and invite international participation in such a gathering at as early a date as is regarded as opportune, and direct the secretary of the American College of Physicians to formally advise the State Department of this endorsement.

"AND BE IT FURTHER RESOLVED, That the president of the American College of Physicians is authorized and empowered to appoint a Fellow of the American College of Physicians to represent the American College of Physicians on a committee composed of duly authorized and appointed representatives of the Association of American Physicians, American Public Health Association, American Academy of Tropical Medicine, American Society of Tropical Medicine, National Malaria Society, American Society of Parasitologists, Southern Medical Association, American Medical Association, American College of Physicians, American Association for the Advancement of Science, and the Section on Medical Science of the National Research Council, to meet on call from the president of the American Academy of Tropical Medicine, for organization, and in their organized capacity to assist the State Department in developing, promoting and holding such a congress, and the American College of Physicians will further give all practicable support to the realization of this project."

The Committee recommends that these resolutions be adopted by the Board of Regents, and I so move.

. . . The motion was seconded and passed and subsequently, President David P. Barr appointed Dr. Joseph M. Hayman, Jr., F.A.C.P., Cleveland, as the College representative. . . .

DR. LEE (Continuing): Referred business from the Board of Regents. At the last meeting of this Board, November 18, 1945, the Board of Regents referred to the Committee on Public Relations a consideration of whether to extend College membership beyond North America and its possessions. The present policy is to restrict membership to North American countries and their dependencies and, further, to physicians who speak or read English. The Secretary reports that the reason for this action was due to a feeling that a man who can neither speak nor read English would contribute little to the College and receive but little value from his College membership. He would seldom attend meetings or participate in College activities. The College has no machinery under its present By-laws whereby candidates from other countries can qualify. The Committee discussed this matter at length and voted that this referred business be continued and referred to this same Committee, or successor Committee, for further study and adoption. The Committee feels it is not now the time, probably, to adopt any change in the policy, but likely in the future there may be some change which would make this desirable. The Committee recommends

without prejudice that this item of business be continued on the agenda of the next Committee on Public Relations and I so move.

. . . The motion was seconded and carried. . . .

... Likewise, a motion to adopt the report as a whole was seconded and carried. . . .

CHAIRMAN IRONS: We will now have the report of the Committee on Finance by Dr. Lee, Chairman.

DR. LEE: The Finance Committee had a meeting at which the President of the College, the Executive Secretary and the Treasurer were present.

1. The financial status of the College seemed to be entirely satisfactory. The Executive Secretary reports that the income from the Technical Exhibits will more than cover the expenses of this meeting.

2. The final financial report of 1945 was published in the April 1946 issue of the ANNALS OF INTERNAL MEDICINE; likewise, the Auditor's official report. I move that the financial report as published and the Auditor's report be accepted.

. . . The motion was seconded and carried. . . .

DR. LEE (Continuing): There were various security transactions since the last meeting of this Board. Under the By-laws the Board of Regents should give specific approval to changes in the Endowment Fund and, therefore, I present the Endowment Fund changes.

Sales

ENDOWMENT FUND				<i>Cost</i>	<i>Sold For</i>	<i>Gain</i>
12- 6-45	5,000	Great Northern Railway, Gen. Mort., Series "B," 5 1/2s, due 1952		\$4,463.45	\$6,060.00	\$ 1,596.55
12- 6-45	5,000	Pennsylvania Railroad, Gen. Mort., Series "E," 4 1/4s, due 1984		5,013.10	6,385.00	1,371.90
1-29-46	50	Shares Johns-Manville Corp., common		4,789.55	7,220.80	2,431.25
						<u>\$ 5,399.70</u>

Purchases

ENDOWMENT FUND		
1-29-46	80 Shares, Ingersoll Rand Co., common	\$11,243.10
1-29-46	7,000 United States of America Savings Bonds, Series "G," 2 ½s, due 1958	7,000.00
2-20-46	100 Shares, Houston Light & Power Co., common	8,837.80
4-25-46	6,000 American Tobacco Co., 3s, due 1969	6,375.00
4-27-46	50 Shares, American Smelting & Refining, 7%, Pfd.	9,517.80

These transactions have already taken place and I move they be approved by the Board of Regents.

... The motion was seconded and carried. . . .

DR. LEE (Continuing): There are also other transactions for the General Fund which I am now reporting for your information.

Sales

GENERAL FUND		Cost	Sold For	Gain
12- 6-45	5,000 Chicago, Burlington & Quincy R. R. Co., Gen., 4s, due 1958	\$4,893.75	\$5,897.50	\$ 1,003.75
12-28-45	100 Shares, Curtiss-Wright Corp., Class A	2,652.80	2,776.08	123.28
				<u>\$ 1,127.03</u>

Purchases

GENERAL FUND

2- 7-46 50 Shares, Continental Can, 3 $\frac{3}{4}$ s, Pfd. \$ 5,601.75

It is also contemplated that the following securities shall be purchased from the cash receipts at the present time. One-half the bonds of the Oregon-Washington Railroad will be purchased for the Endowment Fund account.

Security	Annual Dividend	Approximate Current Market	Yield	Cash Value	Annual Cash Income
SUGGESTED PURCHASES					
\$10,000 OREGON-WASHINGTON RAILROAD & NAV. First 3s, 10/1/60 (Call. @ 104 $\frac{1}{2}$; for S.F. @ 102 $\frac{1}{4}$)		105 $\frac{3}{4}$	2.53%	\$10,575	\$300
200 shs. COMMONWEALTH EDISON Co., Common	\$1.40	36	3.89	7,200	280
100 shs. PHILADELPHIA ELECTRIC Co., Common	1.20	30	4.00	3,000	120
				<u>\$20,775</u>	<u>\$700</u>

I move the approval of the Board of Regents for these purchases, specific with regard to the Endowment Fund item.

. . . The motion was seconded and carried. . . .

DR. LEE (Continuing): Additions required to the 1946 Budget:

. . . By individual resolutions, the following additions to the 1946 budgets were approved, after detailed review by Dr. Lee:

\$ 300.00 Editor's Office
 - 1,150.00 Educational Director's Office (deficit to June 1)
 2,500.00 Executive Secretary's Office.

. . . By resolution, the report of the Finance Committee was approved as a whole.

. . . CHAIRMAN IRONS: The Treasurer will not make a report at this time because he feels that the Finance Committee has adequately covered all that he would have to report. The next item is an announcement about exhibits.

SECRETARY LOVELAND: I just want to ask that members of the Board of Regents, if they have time, go through our Technical Exhibits. I am dependent upon advice from our Committee on Exhibits, Drs. Piersol, Wolferth and Klein. Our exhibits are selected carefully. We want your interest and advice. The exhibits produce a considerable income, about \$21,000.00 this year. You will see nothing in our exhibit that is so commonly seen at the exhibits of other medical societies. We accept nothing that is irrelevant to the practice of medicine. There are no cigarettes, soft drinks, bananas and all sorts of irrelevant items displayed at many other meetings. We try to keep our exhibit on a high plane in every regard. We have published a bulletin about the exhibits which is distributed to every registrant. I would like to have your interest in the exhibits because we have a long range program. Furthermore, your interest as Regents of the College will mean much to the exhibitors.

. . . The meeting by resolution was adjourned. . . .

Attest: E. R. LOVELAND
Executive Secretary

MAY 17, 1946

The third meeting of the Board of Regents during the Philadelphia Annual Session convened in Room 101, Philadelphia Convention Hall at 12:40 p.m., Dr. David P. Barr, the new President, presiding and Mr. E. R. Loveland acting as Secretary. The following were present:

David P. Barr
 Hugh J. Morgan
 James J. Waring
 A. B. Brower
 T. Homer Coffen
 William D. Stroud
 George Morris Piersol
 Francis G. Blake
 James F. Churchill
 Charles T. Stone
 Walter B. Martin
 LeRoy H. Sloan
 George F. Strong
 Ernest E. Irons
 T. Grier Miller
 Charles F. Moffatt
 Chauncey W. Dowden

President
 President-Elect
 First Vice President
 Second Vice President
 Third Vice President

Chairman, Board of Governors

PRESIDENT DAVID P. BARR: It is a pleasure to welcome to this Board Dr. Charles F. Moffatt, Dr. William S. McCann and Dr. T. Grier Miller.

For the first business of the day, we wish to discuss the meeting place for next year, and I will ask the Executive Secretary to present invitations.

SECRETARY E. R. LOVELAND: We do not have the usual quantity of invitations, but it will not be necessary to read all of the letters. We have formal invitations from St. Louis and from Chicago, supported by letters from the local medical societies and other agencies. It is obvious that we should discuss these two invitations, because it is assumed that our next meeting should be held westward, for it has been our custom to alternate between the east and middle west. These two invitations are official and they are complete.

MEMBER: I would like to say a word for St. Louis. I know the standard of clinic and clinical facility arrangements would be adequate. In talking with the Convention Bureau there, however, it appears that St. Louis, at the present time, is not able to offer a sufficient number of hotel rooms. Recently St. Louis entertained the Association for the Advancement of Science. I was interested to hear from the Convention Bureau on that, and they told me they accommodated 2,500 people, but they explained that they doubled them up three or four in a room, and they do not feel that they could treat members of the American College of Physicians that way. I feel it is not feasible to consider St. Louis for next year.

DR. LEROY H. SLOAN: Mr. Chairman, in consultation with the Convention Bureau and hotels of Chicago we have found that, at particular times, Chicago seems to be perfectly ideal. We have been assured that Chicago will furnish an adequate number of rooms for our members and guests. The Chicago Convention Bureau assumes full responsibility and has sent a representative here to talk about their facilities and to answer questions.

We contacted the dean of every medical school and college, the superintendent or medical director of each hospital, and others that were particularly interested in this

Convention. We have received a reply from every one to whom a letter was sent, heartily welcoming us and promising to do everything to make the meeting a success.

PRESIDENT BARR: May we have a report from the Chicago Convention Bureau?

MR. FRANK POWER (Chicago Convention Bureau): We can accommodate you with 2,000 to 2,500 rooms, if necessary. I represent the Convention Bureau and the hotels as a whole. It is our plan to have one centrally located hotel in Chicago as headquarters, and I shall attempt to place all of your members and guests in two or three hotels within a block or so from the headquarters hotel. I am thinking of the Palmer House, the Stevens Hotel and the Congress Hotel. Regardless of what hotel is specified as headquarters, there are many people who prefer to stay at their favorite hotel when in Chicago. We can furnish you with as much, if not more, in the way of facilities than any other city might offer. We will satisfy you in every way possible.

. . . There followed general discussion and considerations about local transportation facilities, clinic and hotel facilities and charges made by hotels for meeting room space. Mr. Power was of the opinion that no charge would be made for meeting space in Chicago. . . .

PRESIDENT BARR: If there are no further questions, we will call for action on the invitation from Chicago.

. . . Upon motion duly made, seconded and carried, Chicago was selected for the 1947 Annual Session. A further resolution was adopted directing that the meeting be held during the latter part of April, but leaving the fixing of final dates to the President, General Chairman and Executive Secretary. . . .

MEMBER: Mr. Chairman, as a suggestion the College meeting might be held the week preceding the meeting of the Association of American Physicians at Atlantic City. Many members come from the western States and if we could arrange the College meeting just preceding the meeting of the Association, it would facilitate matters, allowing our western members to come on east to the Association meeting without first returning home.

. . . A resolution was adopted appointing Dr. LeRoy H. Sloan as General Chairman of the Chicago Session. . . .

PRESIDENT BARR: We must elect a Secretary-General and a Treasurer of the College for 1946-47.

. . . Dr. George Morris Piersol was nominated, seconded and his reelection unanimously approved by resolution. . . .

MEMBER: Mr. President, in passing this resolution I think we ought at the same time to express our very deep appreciation for the wonderful things Dr. Piersol has done for the College for so long a time. There are no words that I can say that would express our gratitude to him. (Applause.)

DR. GEORGE MORRIS PIERSOL: I want to express my gratitude for the confidence placed in me. However, we cannot escape the fact that the time will come when some one else should take over the Secretary-Generalship. As age creeps up, one's ability slows down; secondly, the general principle of having a perennial officer is not a good one for the organization. I want to tell you now, deeply as I appreciate the way in which you have cooperated with me over all these years, I think you should seriously consider the possibility and wisdom of replacing the Secretary-General with a younger and more vigorous man.

PRESIDENT BARR: May we have nominations for the office of Treasurer for 1946-47?

. . . Dr. William D. Stroud was nominated for reelection. Nominations were closed, and he was declared, by resolution, reelected as Treasurer of the College. . . .

. . . President Barr proceeded with the election of the Executive Committee and the appointment of other Committees as follows:

Executive Committee

David P. Barr, New York, N. Y., Chairman
 Hugh J. Morgan, Nashville, Tenn.
 George Morris Piersol, Philadelphia, Pa.
 William D. Stroud, Philadelphia, Pa.
 Francis G. Blake, New Haven, Conn.
 James F. Churchill, San Diego, Calif.
 Chauncey W. Dowden, Louisville, Ky.
 Ernest E. Irons, Chicago, Ill.
 James E. Paullin, Atlanta, Ga.

Committee on Advertisements and Commercial Exhibits

George Morris Piersol, Philadelphia, Pa., Chairman
 Thomas Klein, Philadelphia, Pa.
 Charles C. Wolfert, Philadelphia, Pa.

Committee on the Annals of Internal Medicine

Reginald Fitz, Boston, Mass., Chairman—1947
 Walter B. Martin, Norfolk, Va. —1948 (filling out term of W. W. Palmer)
 T. Grier Miller, Philadelphia, Pa. —1949

Committee on Constitution and By-Laws

James E. Paullin, Atlanta, Ga., Chairman —1948
 Charles F. Moffatt, Montreal, Que., Canada —1949
 George F. Strong, Vancouver, B. C., Canada—1947

Committee on Credentials

George Morris Piersol, Philadelphia, Pa., Chairman—1948	} From the Board of Regents
LeRoy H. Sloan, Chicago, Ill. —1947	
A. B. Brower, Dayton, Ohio —1949	
J. Edwin Wood, Jr., University, Va. —1948	} From the Board of Governors
*George H. Lathrope, Newark, N. J. —1947	
Wallace M. Yater, Washington, D. C. —1949	

Committee on Educational Policy

William S. Middleton, Madison, Wis., Chairman
 Francis G. Blake, New Haven, Conn.
 Hugh J. Morgan, Nashville, Tenn.

Advisory Committee on Postgraduate Courses

(Appointees of the Board of Governors)

Edward L. Bortz, Philadelphia, Pa., Chairman
 Edgar V. Allen, Rochester, Minn.
 Turner Z. Cason, Jacksonville, Fla.
 Ernest H. Falconer, San Francisco, Calif.
 James J. Waring, Denver, Colo.

Committee on Fellowships and Awards

Reginald Fitz, Boston, Mass., Chairman
 T. Homer Coffen, Portland, Ore.

* Appointed by Board of Governors to complete term of J. Owsley Manier, resigned.

William S. McCann, Rochester, N. Y.
 Hugh J. Morgan, Nashville, Tenn.
 James J. Waring, Denver, Colo.

Committee on Finance

Charles F. Tenney, New York, N. Y., Chairman—1948
 Roger I. Lee, Boston, Mass. —1947
 Charles T. Stone, Galveston, Tex. —1949

Committee on Nominations

James J. Waring, Denver, Colo., Chairman —Regent
 George F. Strong, Vancouver, B. C., Canada—Regent

Ralph A. Kinsella, St. Louis, Mo. —Governor
 Asa L. Lincoln, New York, N. Y. —Governor

Jonathan C. Meakins, Montreal, Que., Canada—Fellow-at-Large

Committee on Public Relations

Roger I. Lee, Boston, Mass., Chairman —1947
 Ernest E. Irons, Chicago, Ill. —1950
 James E. Paullin, Atlanta, Ga. —1949
 George F. Strong, Vancouver, B. C., Can.—1948
 David P. Barr, New York, N. Y. —Ex Officio

Committee on Post-War Planning for Medical Service

George Morris Piersol, Philadelphia, Pa., Chairman
 Edward L. Bortz, Philadelphia, Pa.
 Ernest E. Irons, Chicago, Ill.
 LeRoy H. Sloan, Chicago, Ill.

PRESIDENT BARR: We have had no recent information regarding the Committee on Post-War Planning for Medical Service, of which Dr. Piersol is the Chairman. Is it an active Committee?

DR. PIERSOL: That Committee is a group representing the College on the Central National Committee, which meets almost monthly in Chicago. Many groups are represented on the Central Committee. It is still in existence.

DR. ERNEST E. IRONS: I, with Dr. Piersol, have represented the College at several meetings of that Committee. The development of more activity is quite the feeling among most of those organizations represented. I think our College might very well be continued, perhaps in a little different form, on this Post-War Medical Committee, because it will be very helpful at our next meeting. This Central Committee is a sort of clearing house and a very important front for all medicine. It has been gratifying to see the amount of coöperation that has been obtained among these different organizations. The Committee has had, as a rule, twenty to thirty members in attendance, and I have been amazed at the desire and willingness of these people to come from all over the country. We have all kinds of problems with which to deal.

PRESIDENT BARR: We shall continue the Committee with Dr. Piersol as Chairman, and I may later appoint another member to take Dr. Walter W. Palmer's place, for he is no longer a member of this Board.

Conference Committee on Graduate Training in Medicine

Reginald Fitz, Boston, Mass., Chairman
 LeRoy H. Sloan, Chicago, Ill.

Consulting Committee on Annual Sessions

David P. Barr, New York, N. Y., Chairman
 LeRoy H. Sloan, Chicago, Ill.
 Ernest E. Irons, Chicago, Ill.
 George Morris Piersol, Philadelphia, Pa.
 James E. Paullin, Atlanta, Ga.

Council for Study, Prevention and Treatment of Rheumatic Fever

Hugh J. Morgan, Nashville, Tenn.
 William D. Stroud, Philadelphia, Pa.

PRESIDENT BARR: I should like to ask about the Council for Study, Prevention and Treatment of Rheumatic Fever, which was formed as a result of a resolution to appoint two representatives and to appropriate a fund of \$1,000.00 by the College.

DR. HUGH J. MORGAN: I attended, as the representative of the College, a meeting of this so-called Council on Rheumatic Fever, which was sponsored by the American Heart Association. I am sorry to say I have no report to make, other than to state that the meeting was called to make plans to obtain funds, which would be made available for research on rheumatic fever.

PRESIDENT BARR: We will leave this Committee on the books, but we shall expect a report on it at the next meeting of this Board.

House Committee

William D. Stroud, Philadelphia, Pa., Chairman
 T. Grier Miller, Philadelphia, Pa.
 Charles L. Brown, Philadelphia, Pa.

Survey Committee

William S. Middleton, Madison, Wis., Chairman	} From the Board of Regents
James E. Paullin, Atlanta, Ga.	
George Morris Piersol, Philadelphia, Pa.	} From the Committee on Credentials
Wallace M. Yater, Washington, D. C.	
George H. Lathrope, Newark, N. J.	} From the Board of Governors

American Board of Internal Medicine—In accordance with the report from the Chairman of the American Board of Internal Medicine, the Board of Regents nominated the following Fellows as representatives, three of whom shall be elected by the American Board of Internal Medicine and their names and terms of office later reported back to the College:

Alexander M. Burgess, Providence, R. I.
 Richard A. Kern, Philadelphia, Pa.
 William B. Porter, Richmond, Va.
 Roy W. Scott, Cleveland, Ohio
 Wallace M. Yater, Washington, D. C.

... The above elections are occasioned by the expiration of the term of one of the present ACP representatives on the American Board of Internal Medicine and the appointment of two additional members, bringing the total personnel of the Board up to twelve—five of whom will be representatives of the Section on the Practice of Medicine of the American Medical Association and seven of whom will be representatives of the American College of Physicians.

PRESIDENT BARR: Is there any new business?

SECRETARY LOVELAND: Mr. Chairman, a matter has been called to my attention that I would like to mention now concerning our future Annual Business Meetings.

Arranged at the end of the scientific session on Thursday afternoons, they are attended by a small number of Fellows, with the result that a comparatively small number participate in the administration of the College and the selection of its Officers. One of our new Regents made a very practical suggestion, namely, that the Annual Business Meeting be held during an extended intermission in the middle of the Thursday afternoon general session. This would insure an adequate attendance and, obviously, create a wider interest in the meeting.

DR. GEORGE F. STRONG: At the last meeting of the Board of Regents the matter concerning tenure of office of Governors was tabled. I would now like to move that we take it off the table, so that we may reconsider it. I so move, Mr. Chairman.

. . . The motion was seconded and carried. . . .

DR. STRONG: Mr. Chairman, I have spoken to a number of Governors about this matter. The consensus of opinion among them is that there should be some limitation of the tenure of office. I would now like to move that our previous resolution be altered from two consecutive terms to three consecutive terms of three years each.

DR. CHAUNCEY W. DOWDEN: I second the motion.

DR. JAMES J. WARING: Care should be taken to cover the fact that a good many of the members of the Board of Governors have already served two, three, four, or more, terms. Is this motion made for the purpose of allowing them to serve one more term after their present term? There should be a clear understanding of just when this rule will go into effect.

DR. STRONG: My interpretation would be that if this passes, when a man comes up for reelection in the future, if he has served nine consecutive years, he is not eligible for reelection.

PRESIDENT BARR: Probably about one-third of the Governors would be affected.

DR. MORGAN: I think it would be helpful to a new Governor coming into office if he had a year's experience, or at least one Annual Meeting, prior to his taking over the responsibility of Governor.

DR. STRONG: My supplementary thought back of my motion is that the matter be referred back to the Committee on Constitution and By-laws, with directions that they prepare a proper amendment providing limitation of office of Governors to three consecutive terms, so that formal action can be taken at the next meeting of the Board of Regents.

. . . The motion was put to vote and unanimously carried. . . .

. . . Upon motion duly made, seconded and carried, the meeting adjourned at 1:40 p.m. . . .

Attest: E. R. LOVELAND,
Executive Secretary

OBITUARIES

DR. CLYDE WALLACE KIRKLAND

Clyde Wallace Kirkland, Ph.B., M.D., Associate of the College by virtue of membership in the old American Congress on Internal Medicine, Bellaire, Ohio, died March 25, 1946, of coronary occlusion; aged 64.

Dr. Kirkland had been Secretary-Treasurer of the Belmont County Medical Society and President of the Board of Trustees of the Belmont County Tuberculosis Sanatorium. He was formerly councillor of the Seventh District of the Ohio State Medical Association and President of the Ohio Public Health Association, 1923-1924. More recently, he served on the staff of the Bellaire City Hospital, where he died.

DR. GROVE P. M. CURRY

Dr. Grove Price Mitchell Curry, an Associate of the American College of Physicians by virtue of membership in the former American Congress on Internal Medicine, Mount Kisco, N. Y., died during May, 1946. He was born in 1866 and thus lived to the age of eighty. In his last communication to the College he said, "It is getting near the sailing time. Life's pilgrimage has no time table."

Dr. Curry received his medical education at New York University Medical College, graduating in 1892. For a great many years he was a member of the staff of the Northern West Chester Hospital. He was a member of the American Public Health Association, the American Medical Association and a Fellow of the New York Academy of Medicine.

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SCHISTOSOMIASIS JAPONICA: ITS CLINICAL DEVELOPMENT AND RECOGNITION *

By ERNEST CARROLL FAUST, *New Orleans, Louisiana*

SCHISTOSOMIASIS japonica was first recognized clinically almost 100 years ago in Japan, under the name Katayama disease.¹ Fifty-seven years were to pass before the etiological agent was discovered to be a trematode, which was named *Schistosoma japonicum*.² This oriental disease was found to be related to vesical schistosomiasis, the so-called bilharziasis of Egypt, and to be even more closely akin to Manson's schistosomiasis of Africa and of certain tropical areas in the Western Hemisphere. Ten years after the etiology of the disease had been established, it was demonstrated that the life cycle of the parasite, like that of all other trematodes, involves a mollusc, in this case a small, amphibious fresh-water snail.³ Man and other susceptible mammals acquired the infection from wading, bathing or washing clothes in fresh water which was infested with the fork-tailed cercaria, the larval stage of the parasite that escapes from the snail. The snail, in turn, had become infected from the ciliated larvae which hatched from eggs of the parasite after the mammalian host's stools had reached fresh water.^{3, 4, 5}

In addition to five relatively small endemic foci in Japan, schistosomiasis japonica was found to constitute a major disease hazard in China, including practically the entire Yangtze watershed and most of the coastal river valleys south of Shanghai.⁵ Later it was discovered to be present in a small area in Formosa,⁵ to be endemic on four of the larger islands of the Philippine Archipelago⁶ and to exist in at least one small area in Celebes.⁷ Nowhere else in the world has the disease been demonstrated to be indigenous, most probably because the appropriate snails are established only in certain countries bordering on the China Sea.

Japanese physicians in endemic areas studied patients who almost without exception were repeatedly exposed to infection from early childhood to middle

* Received for publication June 1, 1946.

From the Department of Tropical Medicine, Tulane University, and Commission on Schistosomiasis, Commission on Tropical Diseases, Army Epidemiological Board, Preventive Medicine Service, Office of the Surgeon General, U. S. Army, Washington, D. C.

life or later. They suffered from hepatomegaly⁸ or hepatic cirrhosis,⁹ frequently with marked ascites¹⁰; splenomegaly,⁸ anemia,¹¹ appendicitis¹² and at times Jacksonian epilepsy.¹³ Postmortem examination demonstrated extensive granulomata of the bowel; nodular periportal fibrotic lesions and pipe-stem cirrhosis of the liver; an enlarged, firm, at times fibrotic spleen; granulomata of the brain, and occasional carcinoma of the liver or colon. In a few American and European patients in China, who were observed within a few weeks to months after a single, or at most only a few contacts with infested water, the cardinal symptoms and signs of the disease were urticaria, angioneurotic edema, an evening rise in temperature, eosinophilia and dysentery.^{14, 15, 16, 17, 18} On the other hand, Chinese patients with multiple exposure, who consulted Western practitioners late in the disease, had symptoms of advanced intestinal disorders and hepatic cirrhosis.¹⁹ Similar findings of chronic infection were reported by internists, surgeons and pathologists in the Philippines.²⁰

Schistosomiasis japonica has until recently been almost a medical curiosity to all American physicians except those who have practiced in endemic areas in China. However, several years ago Bovaird and Cecil²¹ studied two cases in New York, one a Japanese who came to necropsy and one an American youth who had contracted the disease in the Yangtze Valley, China. Even schistosomiasis mansoni, which parasitizes approximately 10 per cent of the population of Puerto Rico, has been relatively unknown to the medical profession in the United States.

When American military forces invaded Leyte, P. I., on October 20, 1944, they established beachheads on the East Shore and in the Leyte Valley, possibly the most highly endemic center of schistosomiasis in the Orient. Medical and sanitary officers were cognizant of the dangers of the disease and the way in which it is contracted but at the time the known ways of guarding against exposure were for the most part impractical, particularly for certain engineering companies who were under orders to rebuild bridges over the several rivers which empty into Leyte Gulf. During a period of approximately four to five months following invasion day a considerable number of troops, including both combat and service forces, acquired the infection. Some of the men developed very heavy infection, more were suffering from a moderately severe variety of the disease, while probably the largest number of all had mild symptoms or were temporarily asymptomatic. A year after the first exposure more than 1000 cases had been studied in Army General Hospitals in the United States, and the guess is ventured that a considerably larger group have thus far escaped diagnosis.

Many of the service men who may have been exposed on Leyte before control measures became effective have already been discharged from the armed forces and have resumed their place in civilian life. It is possible that some of these men may eventually develop symptoms and require a physician's care. Thus, it is a matter of concern that physicians in Veterans Facilities or in civilian practice be acquainted with the usual train of

symptoms and potential sequelae attendant on infection with *Schistosoma japonicum*.

THE PATHOGENESIS OF SCHISTOSOMIASIS JAPONICA

An understanding of the clinical manifestations of schistosomiasis requires basic knowledge of the pathogenesis of the disease from the time of exposure until the chronic stage has developed. Whenever the small but energetic fork-tailed larvae of *Schistosoma japonicum*, *S. mansoni* or *S. haematobium* come in contact with human skin, as the water drains off or begins to evaporate the larvae drop their tails and start to bore and digest their way into the epidermis. Within a few minutes they are safely under the skin's surface but require several hours to burrow down to the cutaneous blood capillaries, which they enter between the sixteenth and twentieth hour. Unless they are temporarily trapped in cutaneous lymph nodes they produce very little tissue reaction (figure 1).

The young worms are passively transported through the chambers of the right heart to the pulmonary arterioles. Unlike hookworm larvae they proceed to squeeze through the capillary net-work into the venules and thence are transported through the left side of the heart into the systemic arterial circulation. A period of approximately four days is required for passage through the lungs, during which time considerable eosinophilic, epithelioid and giant cell reaction is called forth immediately around the paths of migration (figure 2). Furthermore, some larvae break out of the pulmonary capillaries and arrive at blind ends in the tissues. In addition to producing petechial hemorrhage they disintegrate and provoke an acute cellular infiltration.

Most of the larvae which reach the arch of the aorta are carried through the thoracic artery into the abdomen, although some may enter the carotids and the arteries supplying the upper part of the trunk. Only those survive which reach the mesenteric artery and pass through the capillaries into the portal vein. They apparently feed for the first time after their arrival in the mesenteric-portal blood, which is rich in glucose. All larvae which are filtered out in other capillaries become foreign-body emboli and set up both local and systemic reactions. At each site of infiltration a minute miliary lesion develops as a result of the presence of foreign protein. The degree of this reaction depends both on the amount of initial exposure and on the reactivity of the individual who has become infected.

On reaching the portal vein the microscopic larvae pass into the intra-hepatic portion of the vessel, where they feed on whole blood and grow for approximately 16 days. During this period they are discharging an increasing amount of metabolites which cause an acute local inflammatory reaction in the liver and a general systemic reaction.

Now the adolescent worms begin to migrate out to the smaller mesenteric veins. *Schistosoma japonicum* proceeds for the most part to the intestinal wall drained by the superior mesenteric vein; *S. mansoni* to the lower

PLATE I

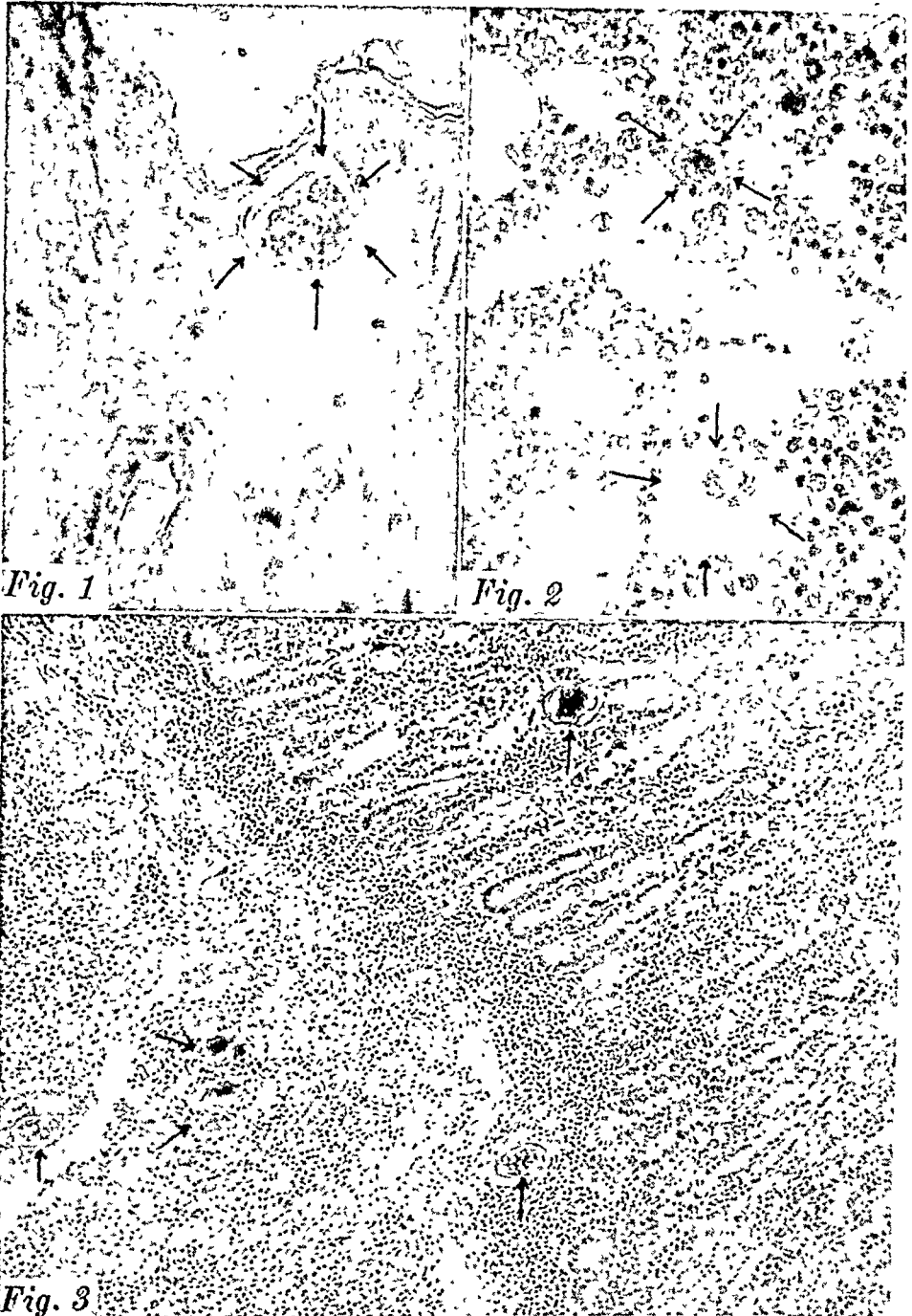


FIG. 1. Section of skin of experimental mouse showing cross section of *Schistosoma* cercaria which has penetrated under epidermis en route to cutaneous venules. Note absence of tissue reaction. $\times 400$. (Original.)

FIG. 2. Section of lung of experimental rabbit showing pulmonary capillary and alveoli five days after exposure to *Schistosoma* infection. The migrating larvae have probably already passed into systemic circulation. Note infiltration of eosinophiles and two giant cells near the capillary. $\times 400$. (Original.)

FIG. 3. Eggs of *Schistosoma japonicum* filtering through submucous and mucous coats of the colon. Section from postmortem of American soldier who had been exposed to infection approximately three months previously. Note mechanical damage but relatively mild tissue reaction. $\times 83$. (Original.)

branches of the superior mesenteric and the branches of the inferior mesenteric vein, and *S. haematobium* through the inferior mesenteric and the pudendal or hemorrhoidal anastomoses to the vesicle venules. The time involved for these migrations is roughly related to the respective distances from the intrahepatic portal vessel: for *S. japonicum* this requires from one to two weeks; for *S. mansoni*, three to four weeks, and for *S. haematobium*, seven to nine weeks. Soon after their arrival in the sites of choice the worms become sexually mature, mate and the females are ready to oviposit.

Egg-laying is accomplished while the delicate female, with her anterior end directed towards a capillary, is held in position in a venule by a male. The egg is considerably larger than the normal diameter of a small venule, so that several eggs typically layed one behind another cause a distention at each site where an egg becomes lodged, with intermediate constrictions between the eggs. Thus, congestion of blood occurs in the capillaries and arterioles blocked by the eggs. Complete embryonation occurs within a short time after the eggs are deposited. Each egg now contains a ciliated larva which is already secreting a viscous lytic fluid that oozes through minute pores in the egg shell and on contact weakens the wall of the venule. The congestion of blood in the capillaries and arterioles and the digestive ferment secreted through the egg shell, together with the characteristic muscular contraction of the wall of the intestine (or bladder), combine to cause rupture of the blood vessel and escape of the eggs in small pools of blood. Before long a considerable proportion of these eggs are filtering through to the lumen of the intestine (or bladder) (figure 3), to be evacuated in a dysenteric stool (*S. japonicum*, *S. mansoni*) or in small flecks of blood and cellular detritus in the urine (*S. haematobium*).

Egg-laying continues unabated during the long life span of the worms. Before many weeks have elapsed some of the eggs have become temporarily lodged in the submucous and muscular coats of the organ, with the development of an enveloping pseudo-abscess, which at times may be expelled from the bowel wall *in toto* but more frequently becomes transformed into a pseudo-tubercle. Soon thereafter in schistosomiasis mansoni, and to an even greater extent in schistosomiasis japonica, some eggs escape into the larger mesenteric venules. These are carried into the liver, where they filter out periportally and soon become centers for pseudo-tubercle formation (figure 4). Others are diverted into collateral venous circulation and may reach the lungs, where they provoke similar tissue reaction (figure 5); or they may get out of the closed venous circulation and come to lodge in cutaneous arterioles (figure 6) or in cerebral vessels (figure 7).

In a few months thousands of eggs may be deposited by a single female *Schistosoma japonicum*. More and more they are permanently trapped in the tissues and become centers of fibrous encapsulation. As a result the intestine loses its vital tissues and develops papillomata and cicatrices, and the liver becomes transformed from an enlarged, inflamed organ into one with periportal fibrosis. With increased embarrassment of blood flow

PLATE II

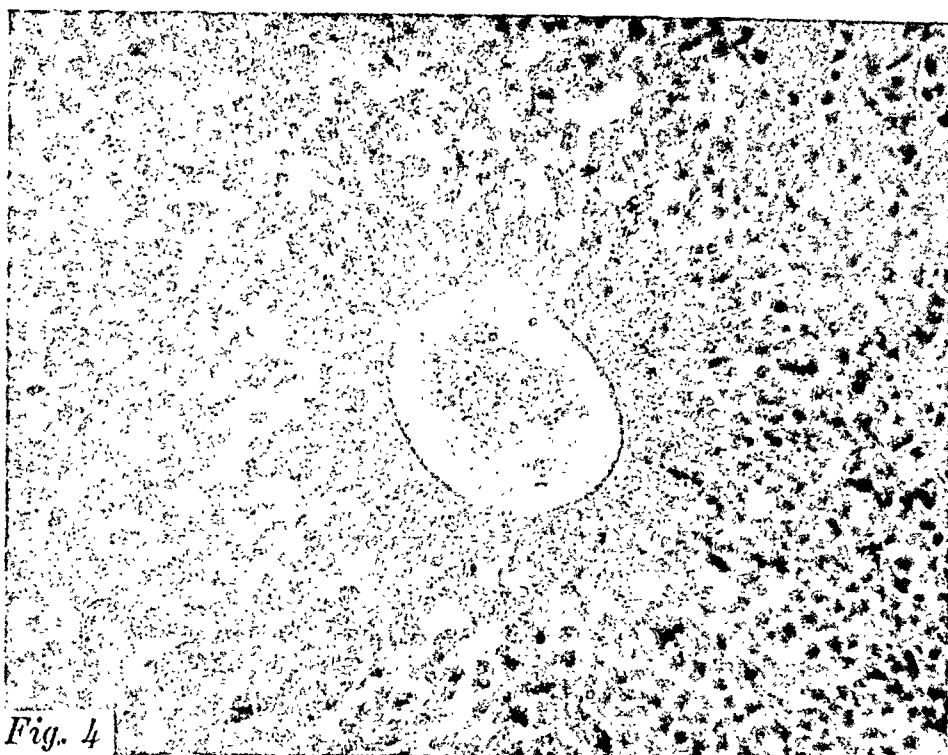


Fig. 4

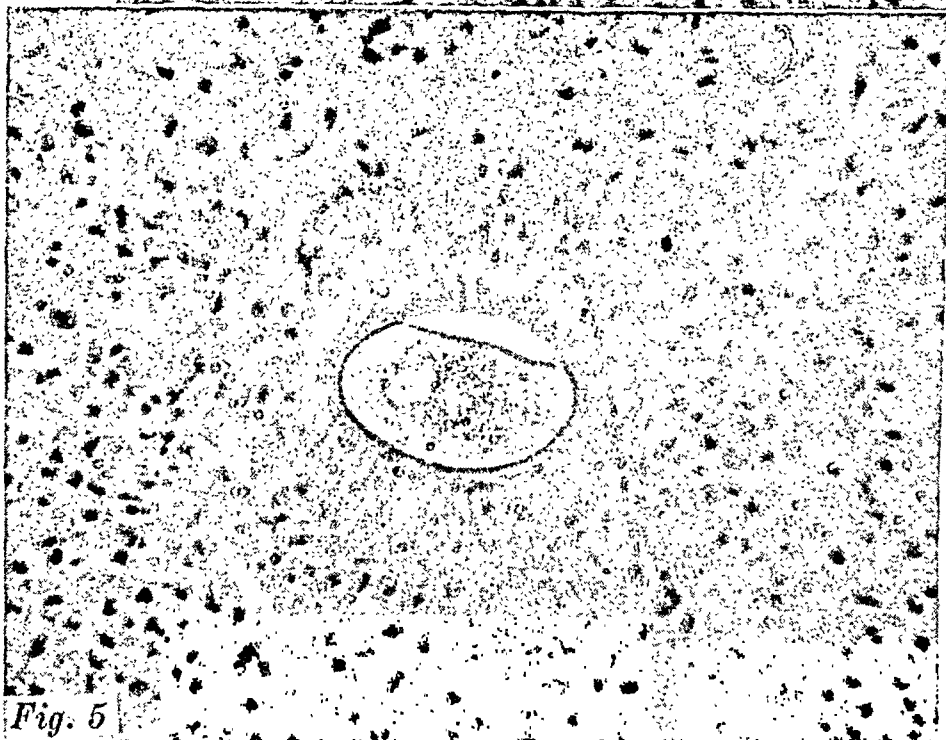


Fig. 5

FIG. 4. Egg of *S. japonicum* containing mature larva which has infiltrated periportally into liver tissue. Note rays of mucoid material which has been secreted by larva and is exuding through the egg shell, together with inflammatory reaction around egg. From the same case as figure 3. $\times 300$. (Original.)

FIG. 5. Egg of *S. japonicum* containing mature larva which has infiltrated from a pulmonary arteriole into the parenchyma. Note streaming rays of mucoid material and cellular reaction around egg. From the same case as figure 3. $\times 400$. (Original.)

PLATE III



Fig. 6

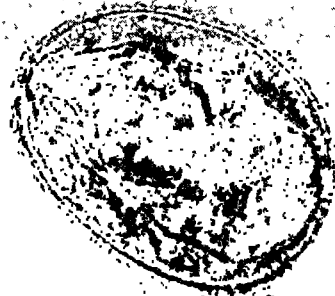


Fig. 8

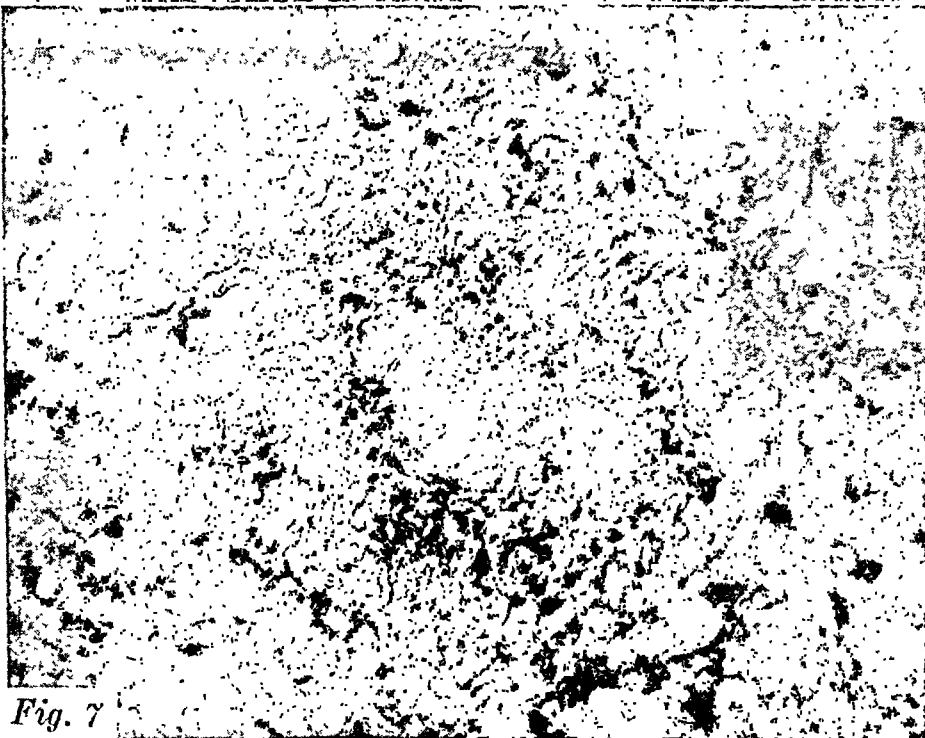


Fig. 7

FIG. 6. Egg of *S. japonicum* which has escaped from a cutaneous intercostal arteriole, with marked cellular infiltration into the area. $\times 200$. (Photomicrograph from section of biopsied specimen, courtesy of Major H. M. Fishbon, M. C.)

FIG. 7. Pseudotubercle formation around egg of *S. japonicum* in granuloma removed surgically from right temporo-parietal area of patient who had been exposed on Leyte, P. I. Mallory stain. $\times 400$. (Original from section provided through courtesy of Major I. Joshua Spiegel, M. C.)

FIG. 8. Mature viable egg of *S. japonicum* recovered from stool of patient on Leyte, P. I. $\times 450$. (Photograph by 3rd Photographic Unit, Army Medical Museum for the Commission on Schistosomiasis.)

through the liver an attempt is made to care for the return of visceral blood through collateral circulation. The spleen becomes passively congested, increases greatly in size and develops a certain amount of fibrosis. The superficial abdominal veins also become greatly distended, while in many late chronic cases ascites results. The increase in the mass of the intestines and the spleen pushes the diaphragm upwards and decreases intrathoracic volume. The lesions resulting from malnutrition and systemic intoxication become increasingly prominent.

THE DEVELOPING SYMPTOMS AND SIGNS IN SCHISTOSOMIASIS JAPONICA

During the biological incubation period, from the entry of the larval worms into the skin until they have matured and egg-laying is about to begin, the symptoms and signs of the disease are due primarily to the intimate contact of the parasites and their metabolites with the tissues in the immediate vicinity of the blood vessels through which the worms are migrating or in which they are temporarily lodged. In addition, the systemic absorption of the by-products account for the more generalized allergic manifestations.

A needling local pain may or may not attend the rapid penetration of the microscopic organisms into the skin but there is seldom an associated dermatitis. During the somewhat longer period when the larvae are squeezing through the pulmonary capillaries, and presumably even to a greater degree when some of them escape into the alveoli, there is bronchial irritation, with an unproductive cough or at times with a discharge of small flecks of dry mucus. There appears to be no special symptom associated with the passage of the larvae through the mesenteric capillaries but those which become lodged as foreign protein emboli in other viscera may be responsible for a relatively early urticaria.

The growing worms in the intrahepatic portal vessel gradually produce inflammation of the liver, with resultant pain in the upper right abdominal quadrant under the costal margin. About the third or fourth week following exposure this organ typically becomes palpable on deep inspiration and pressure over the area elicits acute pain. Meanwhile the adolescent worms are migrating towards the bowel wall and their activity causes a feeling of general abdominal fullness and discomfort. The irritation to the intestinal wall produces a mucus diarrhea which is prodromal to the symptoms initiated by egg deposition. In this terminal stage of the incubation period by-products of the parasites are swept back in portal blood into the liver, which now becomes more acutely tender and continues to increase in size. It is firm but has a smooth surface and rather sharp edges.

The systemic manifestations during the latter part of the incubation period are those resulting from the cumulative absorption of the worms' metabolites. There are gradually increasing malaise, anorexia, nausea and possibly vomiting. Rather frequently stiffness and aching develop in the joints and muscles, or along nerve tracts, especially in the region of the neck, back and legs. The patient may wake up in the morning with intense

giant urticaria, an associated edema involving the subcutaneous tissues and mucus membranes, or with a suggestion of angioneurotic edema, whereas the night before there had been no evidence of an allergic condition. Moreover, dermatographia is relatively characteristic at this time. Transient areas of dullness and râles in the lungs, due to local edema, are revealed by percussion and auscultation. Also characteristically there is an elevation of temperature late every afternoon, a drenching sweat during the night and an afebrile but weakened state the next morning. For the first time the patient realizes that he is really sick.

Blood studies at this stage will show no essential change in the red cells but usually a leukocytosis with conspicuous eosinophilia.

The type of case which has been used as an illustration is that of an average adult with moderately heavy, single exposure. Much of the data relating to the earlier part of this stage have been obtained from questioning patients somewhat later in the disease, since they are not likely to have symptoms sufficiently severe to consult a physician until the prodromal period arrives or the acute stage is precipitated. Moreover, a physician is not apt to suspect schistosomiasis during this period unless he has had considerable experience in an endemic area. He is much more likely to consider amebiasis, malaria or infectious hepatitis as possible diagnoses. Even if a diagnosis of schistosomiasis is entertained, it cannot be confirmed until eggs are recovered from the stool.

Several successive exposures or a single massive exposure have probably accounted for the few fulminating infections in American military personnel which have ended fatally. On the other hand, infection may be so light as to be undetected clinically during the earlier stages and may be picked up only after careful stool examination or following some complication.

The second period in the disease is ushered in with egg deposition, which usually begins four to six weeks after exposure. The local and systemic manifestations resulting from irritation caused by the worms and their metabolites continue unabated. Now, however, the irritating effects of the eggs assume the leading rôle as they escape from the venules and filter into the intestinal canal. Traumatic injury to the entire bowel wall, especially the ileum and cecum, provokes hyperperistalsis and tenesmus. The stool may contain more blood and mucus than fecal material, may be unformed and jelly-like in consistency or it may be formed with streaks or clumps of blood and mucus on the outside of the feces. The entire bowel is usually painful and tender. Frequently the appetite and digestion are poor. The patient now experiences considerable loss in weight and his quotidian evening fever persists. He is acutely ill and is compelled to take to his bed.

Physical examination reveals a liver which extends several fingers below the costal margin and a spleen which has become palpable. After complete rest from two to three weeks or longer the patient feels much better and his fever has at least partially subsided. However, when he gets up and

attempts physical exertion the intestinal lesions break down and an exacerbation of acute symptoms occurs.

Throughout this period there is a continued leukocytosis with pronounced eosinophilia, at times as much as 90 per cent of the total white count. If the dysentery has been a prominent symptom, some degree of anemia may be expected.

Patients with moderate exposure may begin to exhibit abdominal tenderness and pain almost as soon as do the more heavily infected ones, but more frequently these symptoms are slower in developing in the lightly infected individuals and may reach clinical grade as late as 10 to 12 weeks or more after exposure. On the other hand, there is some indication that certain individuals with rather mild exposures may react out of all proportion to the number of worms which they harbor, while others with a relatively heavy worm burden have surprisingly mild manifestations.

During this active stage the disease can be diagnosed by the recovery and demonstration of the characteristic eggs (figure 8), which are unequally distributed in the stool and are most likely to be found in masses of blood-tinged mucus. Even though each female worm of *Schistosoma japonicum* lays many more eggs per day than does *S. mansoni*, these eggs may be too few to detect by direct fecal films, so that concentration technics must be employed. Members of the Commission on Schistosomiasis of the Surgeon General's Office²² have found that sedimentation of five-gram amounts of stool in 0.5 per cent glycerinated water, followed by the examination of three cover-glass preparations of the sediment, provides a high degree of assurance of egg recovery from stool specimens containing very few eggs.

In addition to stool examination, pinpoint nodules or distended blood capillaries may at times be visualized by proctoscopy just above the junction of the sigmoid colon and rectum. Removal of specimens of these lesions for direct microscopic observation or section (figure 9) at times provides valuable confirmatory evidence of the disease and occasionally is positive when stool examination is negative.²²

The chronic stage of the disease is already well under way before the active period of egg extrusion subsides. Thus the symptoms resulting from fibrosis are gradually developing while the patient is still suffering from acute inflammation of the liver, diarrhea or dysentery and systemic intoxication. Gradually, almost imperceptibly, the liver begins to shrink as the miliary fibrotic processes around infiltrated eggs increase in numbers. On physical examination the organ feels hard and usually has millet-seed nodules on its surface. Pressure evokes less pain than at an early stage.

The greatly enlarged spleen, which may extend to the umbilicus or into the lower right abdomen, is firm and exquisitely tender. There is considerable thickening of the coils of the small bowel, while the transverse colon gives the impression of irregular enlargement and thickening. As a result of the infiltration of eggs into mesenteric lymph nodes, there may be a

PLATE IV

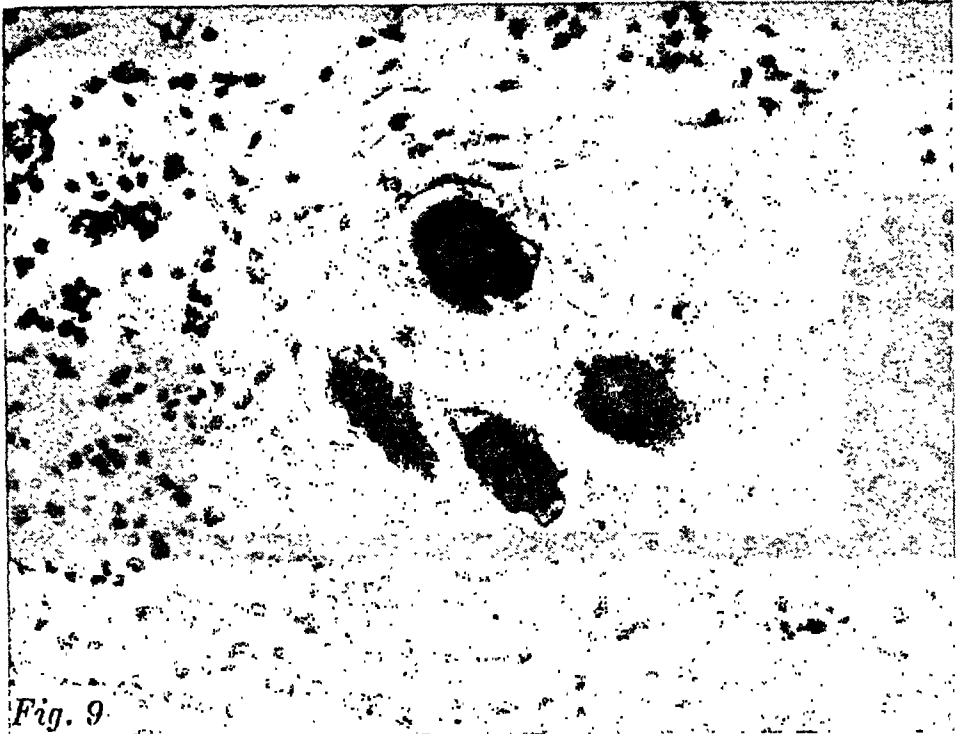


Fig. 9

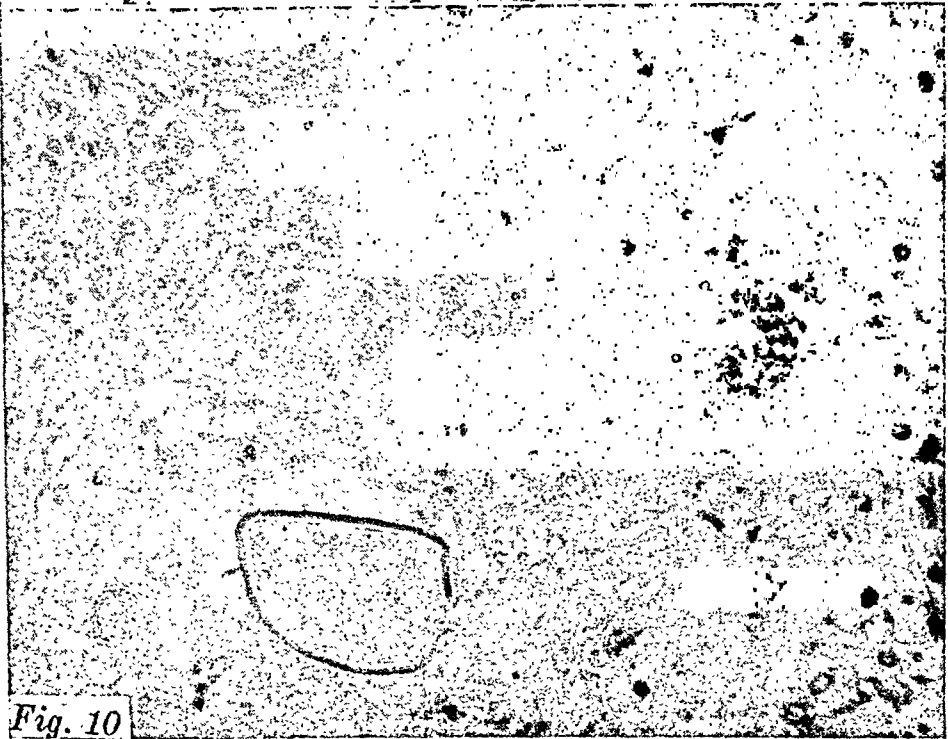


Fig. 10

FIG. 9. Nest of *S. japonicum* eggs in section of biopsied nodule from sigmoid colon. $\times 400$. (Original from section provided through courtesy of Lt. Col. Stuart W. Lippincott, M. C.)

FIG. 10. Shell of *S. japonicum* egg and active foreign body reaction in section from cerebellar granuloma removed post mortem from American veteran. $\times 400$. (Original from material provided through courtesy of Dr. W. L. McNamara, Elmhurst, Illinois.)

mesenteric binding which tends to separate the abdominal viscera into an upper and lower portion. The greatly increased abdominal mass pushes the diaphragm upwards, with corresponding decrease in the size of the pleural cavity. Moreover, some reduction in pulmonary function probably results from the infiltration of eggs in the pulmonary parenchyma. On slight exertion there is pronounced dyspnea.

Generalized abdominal discomfort together with increased digestive dysfunction provides the basis for the dyspeptic condition and the asthenic state. Because of fibrotic scarring of the colon, intestinal stenosis or the development of papillomata, the function of the large bowel is greatly impaired. The elimination of feces becomes irregular, with alternating constipation and diarrhea. At times the infiltration of eggs in the wall of the appendix may provoke an acute appendicitis. Rarely there may be prolapsus recti. Carcinoma of the liver or rectum occasionally develops. Portal obstruction, due to stenosis in the portal venous circulation or to the presence of masses of parent worms which become lodged in a main afferent branch, results in ascites.

During this chronic stage the blood picture shows a decrease in the number of neutrophils. There is usually a persistent eosinophilia, and a characteristic lymphocytosis. Some degree of anemia is now invariably present.

This portrayal of the chronic stage is again that of the average patient. Natives in endemic areas usually give a history of multiple exposures, so that it is difficult to distinguish between those of their symptoms which are due to chronic lesions and those of more recent origin. In any case the advanced chronic condition may be expected to develop in about five years or less after first exposure. If the infection is light the complaints of the patient may be restricted to vague abdominal discomfort and digestive upsets, which are precipitated by physical exertion, alternating with periods of moderate quiescence. In general, it may be stated that for the same amount of infection the symptoms are more severe in *schistosomiasis japonica* than they are in *schistosomiasis mansoni* and that clinical evidence of chronicity develops considerably earlier in the former infection.

Diagnosis of the chronic stage of the disease lies specifically in the same methods as are employed for the acute stage, namely recovery of the eggs. However, the eggs evacuated in the stool at this stage are fewer in number, are discharged with less regularity and are frequently immature or degenerate. Laboratory examination should always include sedimentation of at least one stool specimen.²³ Probably proctoscopic biopsy will be even more useful now than during the earlier stage of the disease. The intradermal reaction with schistosome antigen should be positive,²² while tests demonstrating increased serum globulin will add strong presumptive evidence of *schistosomiasis*. Clinically the condition must be differentiated from hepatic cirrhosis of other etiologies.

COMPLICATIONS RESULTING FROM THE LODGMENT OF SCHISTOSOMA EGGS IN ECTOPIC FOCI

In the Japanese literature on schistosomiasis there are numerous references to neurological complications, especially Jacksonian epilepsy.¹³ In a series of 39 Chinese cases Chu²⁴ reported one with Jacksonian epilepsy and one with hemiplegia. In American patients who contracted the disease on Leyte, P. I., Thomas and Gage²⁵ reported two with neurological lesions. Three others were demonstrated to the writer by Dr. James Bordley, 3rd, at the time he was Commanding Officer of the 118th General Hospital on Leyte. One of these had weakness of the muscles of the left arm, with positive Hoffmann reflex, and transient weakness of the muscles of the left leg and left side of the face. A second patient had flaccid paralysis of the left arm, with positive Hoffmann reflex, right ankle clonus and exaggerated reflexes of the right leg. The third patient, who first developed neurological symptoms six and one-half months after exposure, manifested marked weakness of the muscles of the left side of the body, numbness of the left side of the upper lip and of the left third, fourth and fifth fingers. From time to time, particularly after slight exertion or mild excitement, he exhibited Jacksonian seizures of short duration.

Several additional clinical cases of neurological complications of schistosomiasis have been seen in American Army hospitals both overseas and in the United States. Reports on one of these patients and a diagnosis made post mortem by the writer on another case will be briefly presented.

Clinical Case. (Clinical data and specimen furnished through courtesy of Major I. Joshua Spiegel.) On March 27, 1945, approximately four and a half months after arrival on Leyte, a coast artilleryman, without previous illness, developed a convulsive seizure. The next day there was a second attack preceded by an olfactory aura. From that time he exhibited classical symptoms and signs of a tumor in the right temporo-parietal area, with markedly unilateral choked optic disc. Spinal fluid revealed no abnormalities and repeated stool examinations were negative for parasite objects. He was shortly thereafter evacuated to a General Hospital in the United States. On May 23, 1945 he was operated on and a granulomatous mass about the size of an apple was removed from under the right temporo-parietal bone. Following the operation the patient made an uneventful recovery and there was marked improvement in his left hemiparesis. Section of the tumor mass revealed numerous pseudotubercles around infiltrated eggs of *Schistosoma japonicum*, which the writer was able to confirm on consultation (figure 7). Schistosomiasis had not been suspected until the microscopic slide was examined.

Autopsy Case. (Data and specimen furnished through courtesy of Dr. W. L. McNamara, Elmhurst Community Hospital, Elmhurst, Illinois.) The subject had been in New Guinea and the Philippines for two and one-half years and was discharged on October 20, 1945. He had dengue and benign tertian malaria while overseas, but had not suffered from dysentery. Shortly after his discharge he complained of dull frontal and occipital headache and dizziness, for which he did not seek medical care. He continued to work until five days before his death. On November 25, 1945 he suddenly became comatose. The family physician was called and made a tentative diagnosis of cerebral malaria. The patient died a few hours

later. Autopsy of the brain alone was permitted. A granulomatous mass about 5 cm. in diameter was found in the lateral portion of the cerebellum, which was described as "pearly gray with numerous small foci of softening. It was unencapsulated but the overlying pia mater was thick and nodular." Sections of the lesion were sent for diagnosis to the writer, who found numerous eggs of *S. japonicum* within pseudo-tubercles (figure 10).

In addition to the neurological lesions which have developed in American troops, at least one had cutaneous lesions, first in the abdominal skin and later in the intercostal spaces.²⁶ Biopsy of these lesions revealed typical viable eggs of *S. japonicum* (figure 6). Similar ectopic locations of the eggs have been reported recently from four British soldiers in Nigeria who had acquired *S. haematobium* and *S. mansoni* infection.²⁷

COMMENT AND SUMMARY

As a result of exposure of American troops on Leyte, P. I., opportunity has been provided for the first time to carry out clinical investigation on a considerable number of patients during the early stages of schistosomiasis japonica. These studies have confirmed and materially enhanced the relatively isolated observations on these stages of the disease previously made by investigators in China and elsewhere. The symptoms, signs and physical findings have been somewhat easier to interpret in American military patients than in infected natives, because the disease was contracted within the limits of a few months as contrasted with repeated exposure over a period of years in native patients. Under these relatively ideal conditions for clinical investigation the manifestations have been found to vary qualitatively and quantitatively in different patients, owing to the amount of infection, the reaction of the patient and possibly other, unknown determinants.

There are few clinical landmarks which are in themselves definitely suggestive of schistosomiasis during the prodromal and acute stages, so that diagnosis is relatively hazardous unless there is a definite history of bathing, swimming or otherwise utilizing raw fresh water in a known endemic focus of the disease. The demonstration of the eggs of the parasite constitutes the only known method of specific diagnosis. This requires experience, skill and at times repeated examinations on the part of the laboratory worker. Inexperience has been responsible for incorrect diagnosis and has subjected persons to unnecessary treatment and the anxiety attendant on the belief that the disease had been contracted. Likewise, inexperience has undoubtedly been responsible for failure to find eggs of the parasite when they were probably present in scant numbers in the stools of individuals complaining of vague abdominal symptoms.

Physicians who have been in charge of patients suffering from schistosomiasis are not likely to forget their experience. Those who have not had this opportunity should consider the possibility of this disease in veterans who were on Leyte or elsewhere in endemic foci in the Orient and have returned to civilian life.

BIBLIOGRAPHY

1. FUJII, Y.: Katayama disease (with note), Internat. Med. News, 1847, No. 691 (Japanese text).
2. KATSURADA, F.: Ueber eine endemische Krankheit in der Provinz Yamanashi, Mitt. med. Gesellsch. zu Okayama, 1904, No. 173 (June 30) (Japanese text).
3. MIYAIRI, K., and SUZUKI, M.: Zwischenwirt des *Schistosomum japonicum* Katsurada, Mitteil. Med. Fak. Kaiserl. Univ. Kyushu, 1914, i, 187-197.
4. MIYAGAWA, Y., and TAKEMOTO, S.: The mode of infection of *Schistosoma japonicum* and the principal route of its journey from the skin to the portal vein in the host, Jr. Path. and Bact., 1921, xxiv, 168-174.
5. FAUST, E. C., and MELENEY, H. E.: Studies on schistosomiasis japonica, Am. Jr. Hyg., 1924, Monogr. Ser. No. 3.
6. TUBANGUI, M. A., and PASCO, A. M.: Studies on geographical distribution, incidence and control of schistosomiasis japonica in Philippines, Philipp. Jr. Sci., 1941, lxxiv, 301-327.
7. BRUG, S. L., and TESCH, J. W.: Parasitaire wormen aan het Lindoe Meer (Oa. Paloe, Celebes), Geneesk. Tijdschr. in Nederl.-Indie, 1937, xxxvi, 2151-2158.
8. ISHII, R.: Hypertrophy of liver and spleen of the young people in Yamanashi Prefecture, Yamanashi Pref. Med. Jr., 1900, No. 3 (Japanese text).
9. YAMAGIWA, K.: A case of cirrhosis of the liver, Jr. Tokyo Med. Assoc., 1891 (No. 7) (Japanese text).
10. OZAWA, S.: Endemic ascites, Kyochu Med. Jr., 1896, No. 60 (Japanese text).
11. YOSHIMURA, Y.: Hemolytic action due to the effect of *Schistosoma japonicum*, especially anemia in patients with Katayama disease, Jr. Jap. Path. Assoc., 1913, iii (Japanese text).
12. IWASAKI, K.: Schistosomiasis japonica and the ruptured appendix vermiformis, Jr. Jap. Surg. Assoc., 1911, xi (Nos. 4-6) (Japanese text).
13. YAMAGIWA, K.: Contribution to the etiology of Jacksonian epilepsy. The pathological changes of the cerebral cortex caused by distoma eggs, Jr. Tokyo Med. Assoc., 1889, iii (No. 18) (Japanese text).
14. LAMBERT, A. C.: Notes on some cases of fever with urticarial rash, occurring in the Yangtze Valley, Trans. Soc. Trop. Med. and Hyg., 1910, iii, 278-302.
15. LAMBERT, A. C.: Fevers with urticaria and eosinophilia, and their relationship to infection with *Schistosomum japonicum*, Trans. Soc. Trop. Med. and Hyg., 1911, v, 38-45.
16. LOGAN, O. T.: *Schistosomum japonicum* infection in an American child, Jr. Trop. Med., 1911, xiv, 133.
17. LANING, R. H.: Schistosomiasis on the Yangtze River, with report of cases, U. S. Naval Med. Bull., 1914, viii, 16-20.
18. KASTEIN, J.: Beobachtungen von gehauften Auftreten von "*Schistosomum japonicum*"—Erkrankungen in Shanghai, Arch. f. Schiffs. u. Tropen. Hyg., 1932, xxxvi, 1-4.
19. HOUGHTON, H. S.: A study of ascites and splenomegaly, China Med. Jr., 1910, xxiv, 244-256.
20. WOOLEY, P. G.: The occurrence of *Schistosoma japonicum* vel *cattoi* in the Philippine Islands, Philipp. Jr. Sci., 1906, i, 83-90.
21. BOVAIRD, D., and CECIL, R. L.: Schistosomiasis japonica: a clinical and pathological study of two cases, Am. Jr. Med. Sci., 1914, cxlviii, 187-206.
22. FAUST, E. C., WRIGHT, W. H., McMULLEN, D. B., HUNTER, G. W., III, BAUMAN, P. M., and INGALLS, J. W.: The Commission on Schistosomiasis. (Preliminary report on investigations in the Philippine Islands and Japan), Unpublished report on file, Office of the Surgeon General, U. S. A.

23. FAUST, E. C., INGALLS, J. W., and SEE, J. K.: The diagnosis of schistosomiasis japonica. III. Technics for the recovery of the eggs of *Schistosoma japonicum*, Am. Jr. Trop. Med., 1946, xxvi, (5).
24. CHU, C. F.: Schistosomiasis japonica in Nanking, Chinese Med. Jr., 1931, lii, 651-664.
25. THOMAS, H. M., JR., and GAGE, D. P.: Symptomatology of early schistosomiasis japonica, Bull. U. S. Army Med. Dept., 1945, iv, (2), 197-202.
26. FISHBON, H. M.: Eggs of *Schistosoma japonicum* in the skin, Bull. U. S. Army Med. Dept., 1945, iv, (4), 373.
27. BLACK, K. O.: Cutaneous schistosomiasis involving *S. haematobium* eggs, Brit. Med. Jr., 1945, ii, 453-456.

AMEBIASIS OF THE LIVER: CLASSIFICATION, DIAGNOSIS AND TREATMENT *

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INTRODUCTION

AMEBIASIS of the liver is a disease of considerable interest and importance. Its protean clinical manifestations make it a difficult diagnostic problem at times, but early treatment has such an important bearing on prognosis that its prompt recognition is important. Unfortunately, most reports have emphasized the clinical picture of amebic abscess, usually a late manifestation of the disease, so that many cases go unrecognized and untreated.

Numerous studies¹ have established the fact that amebiasis of the colon is a relatively common disease in the United States. The incidence is even higher in tropical and subtropical areas, where sanitation is notoriously bad. Surveys among American troops serving in India have revealed infection rates between 20 and 40 per cent.² Obviously, amebiasis is going to be an increasingly important problem when troops serving in heavily infected areas return to this country.

The incidence of liver involvement in amebiasis is not known precisely, but there is good evidence to indicate that it is considerably higher than is generally recognized. Autopsy studies have invariably demonstrated a higher incidence than clinical studies. In a large series of amebic dysentery cases collected from the literature¹ the liver was affected in 36.6 per cent of the autopsied cases and in only 4.86 per cent of the clinical cases. In Payne's³ recent report the liver was involved in 56.7 per cent of 1000 clinical cases of amebic dysentery.

Recent studies have emphasized the early lesions of amebic infection of the liver. Palmer⁴ was able to demonstrate these in 18 out of 19 cases of amebic dysentery coming to autopsy. The marked disparity between the number of cases diagnosed clinically and the number found at autopsy would seem to indicate that clinicians are not sufficiently familiar with the manifestations of this disease. This is especially true with regard to the early phases of the disease about which comparatively little has been written.

Surgical drainage was, for a long time, the treatment of choice in amebic liver abscess, but it was always attended by a disastrously high mortality rate. By the introduction of emetine therapy and, later, closed aspiration, Rogers was able to reduce the rate to very low levels.^{5,6} Today the combined use of emetine and aspiration is the most widely accepted form of treatment.^{1,7} Rogers found emetine alone very effective in the pre-sup-

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purative stage of amebic hepatitis, but felt that aspiration was usually indicated where a frank abscess had developed.⁸ In a few instances, however, emetine alone has proved effective in such cases.^{3, 7, 9}

The following report summarizes personal observations made in 69 cases of amebiasis of the liver studied in two United States Army hospitals in Bengal, India, from May 1943 to February 1945. During that period there were 14,688 admissions and of these 748 were discharged with the diagnosis of amebiasis. The liver was involved in 9.2 per cent of the latter. The records of seven patients transferred to the United States were not available so that the clinical data are based on 62 cases. The results of treatment, however, are known in all 69 cases and have been analyzed.

The purpose of this paper is to present a classification of amebiasis of the liver, based on a detailed analysis of its clinical manifestations and the known facts about its pathology, in the hope that it may simplify diagnosis, and to demonstrate the effectiveness of emetine therapy without aspiration.

CLASSIFICATION

Soon after our first encounters with amebiasis of the liver in India, it became apparent that many of our cases failed to fit the usual clinical picture of amebic liver abscess described in standard texts. A perusal of the scanty literature available to us revealed that types of liver amebiasis other than abscess had been described, but that very little emphasis had been placed on the diagnostic and therapeutic implications of their differentiation.

A consideration of its pathogenesis corroborates the view that there are several distinct types of liver amebiasis. In the evolution of the well described abscess, the liver goes through a number of stages which, when they proceed slowly enough, may be differentiated clinically. The destructive effects of *Entameba histolytica*, leading to abscess formation, are accompanied by reparative processes, so that the disease may progress at varying speeds, may halt at any stage or may even regress. The balance struck between these two opposing forces will depend on host immunity, the number, distribution, and virulence of the parasites and possibly on the effects of alcohol, trauma and bacterial infection.¹

Entamebae histolytica reach the liver by way of the portal vein from a focus of infection in the bowel wall.^{1, 10} There they lodge in the smaller radicles of the portal system. By their lytic action the amebae break through the walls of the veins and invade the connective tissue of the portal triads and then the parenchyma, where they produce small areas of liquefaction necrosis bordered by a thin meshwork of fibrinous strands and minimal round cell infiltration. The destructive process extends concentrically by invasion of amebae along open veins, by the coalescence of multiple small lesions and by infarction due to thrombosis of contiguous intrahepatic portal veins. This leads ultimately to the formation of the typical single amebic abscess. When amebae reach the liver in large numbers and are widespread, multiple abscesses may be produced. Grossly, early liver abscesses may be quite small

and solid. Later, they become gelatinous and finally are filled with characteristic reddish-brown fluid which contains little if any cellular exudate. The acute abscess has no capsule and may extend so rapidly it ruptures into neighboring structures. In the more slowly developing abscess a thick fibrous capsule is produced which limits further extension.

Rogers¹¹ points out that most of the amebae reaching the liver become engulfed in thrombosed interlobular veins and undergo degeneration before they can escape the vessel walls. The process gives rise to a congestion of the liver which can be detected clinically and to which Rogers has given the name pre-suppurative amebic hepatitis.

In a study of 19 cases of amebic dysentery coming to autopsy, Palmer⁴ found a patchy increase of portal connective tissue in 18. These findings were associated to a variable extent with proliferation of the bile ducts, lymphocytic and monocytic infiltration of the portal areas, mid-zonal fatty degeneration and increased pigment in parenchymal and Kupffer cells. He believes this patchy fibrosis represents the healed stage of multiple small amebic abscesses.

The concept of a pre-suppurative stage of amebic hepatitis was not entirely new when Rogers introduced it, as Chevers and Maclean¹² had used ipecacuanha in tropical hepatitis to prevent abscess formation as early as 1886, even before the etiology of the disease was known. Rogers, however, was the first to describe it accurately, and to demonstrate the efficacy of emetine therapy. Later he pointed out that pre-suppurative hepatitis occurs in acute and chronic forms. He found it impossible to differentiate the acute form from multiple small amebic abscesses clinically, but felt it was of no importance since both responded equally well to emetine therapy.⁸

Both clinical and autopsy studies have established acute and chronic forms of amebic liver abscess. Berne⁷ has pointed out that, although textbooks and literature from the Orient stress the chronic form, 58 per cent of the cases he found in Southern California were acute. Of the frank abscesses reported in the present study, all were of the acute type. There is reason to believe that the great preponderance of the chronic form in the Orient is related to the inadequacy of medical facilities there and to the failure of patients to report symptoms early.

In analyzing the 62 cases presented in this report it was found they fell into four distinct groups which were readily differentiated clinically:

Acute amebic liver abscess	7 cases
Acute amebic hepatitis	16 cases
Subacute amebic hepatitis	32 cases
Chronic amebic hepatitis	7 cases

There were no cases of chronic amebic abscess. The acute, subacute and chronic amebic hepatitis cases fell into the corresponding groups of pre-suppurative hepatitis described by Rogers, but it was deemed advisable to drop the term "pre-suppurative" since one could not say with certainty that miliary abscesses or even larger central abscesses did not exist, especially in

the acute hepatitis group. Rogers⁸ suggests that leukocytosis which does not decline appreciably or disappear after one week of emetine therapy indicates the presence of an abscess. This point of differentiation was found to be unreliable in our experience. Leukocytosis subsided in less than a week in several cases of frank abscess, and persisted for longer than a week in many cases of very mild subacute amebic hepatitis.

The acute abscess cases were characterized by liver pain, high fever and frequently by cough. A definite mass was demonstrable in the liver either by palpation or by roentgen examination in every instance. The right lobe of the liver was generally enlarged and exhibited compression tenderness. Abnormal pulmonary findings were frequent. Marked leukocytosis with only slight increase in the percentage of polymorphonuclears was the rule.

The acute hepatitis cases resembled the abscess cases except that no mass could be demonstrated in the liver, liver pain and cough were less common, diarrhea and cramps were more common and leukocytosis was less marked.

The subacute hepatitis cases differed markedly from the others. Only half of them complained of liver pain. Many were admitted because of diarrhea and cramps and were found to have enlarged tender livers. Fever was inconstant and when present was low grade in character and intermittent. Cough and abnormal pulmonary findings were unusual. Leukocytosis occurred infrequently and when present was usually mild.

In contrast to the first three groups of cases, in which symptoms were usually present for less than 10 days, the chronic hepatitis cases were admitted with liver pain of long duration, ranging from two to 12 months. As in the case of subacute hepatitis, fever and leukocytosis were inconstant. Diarrhea was fairly common and cough and abnormal pulmonary findings occurred occasionally.

Although it must be admitted that the classification outlined is open to question since small centrally placed abscesses could not be excluded in the hepatitis groups, the detailed analysis of the data will demonstrate clear-cut clinical differences between them. It must be remembered that cases in one group may advance or regress to another, either as a result of treatment or spontaneously under the influence of factors already discussed.

Classifying these cases makes for a better understanding of the underlying pathology, calls attention to the less commonly recognized forms of the disease and gives some indication of the amount and type of treatment required.

The following case histories will illustrate each of the groups mentioned:

CASE REPORTS

Case 1. Acute Amebic Abscess of the Right Lobe of the Liver (Figure 1).

History. A 47-year old officer was admitted to the hospital on September 4, 1943, complaining of abdominal cramps. Four days before admission there was a sudden onset of generalized abdominal cramps, nausea, and watery diarrhea. He was given bismuth and paregoric with prompt relief. Two days later he developed epigastric

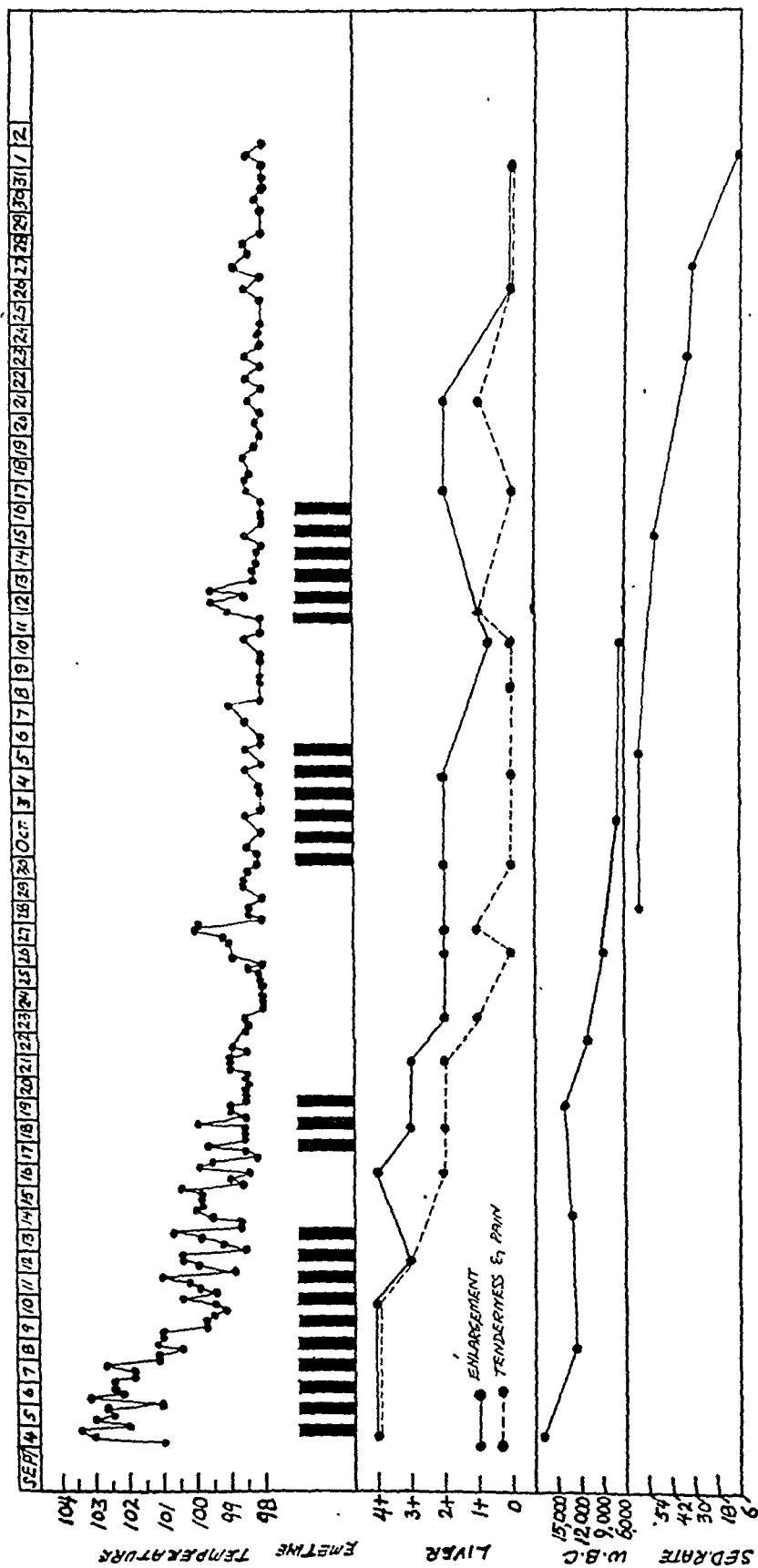


FIG. 1. Case 1. Acute amebic abscess of the right lobe of the liver.

pain, fever, chilly sensations and profuse sweating. The epigastric pain was crampy in character, moderately severe, radiated to the back, and was aggravated by deep breathing, movement in bed and by lying on the left side.

The patient had spent six weeks in China and six weeks in India just prior to the onset of his present illness. Shortly after his arrival in China he had had a mild attack of diarrhea which subsided spontaneously in a few days. He denied previous gastrointestinal symptoms. Alcoholic consumption was moderate. He had lost seven pounds in weight since his arrival in the Orient.

Examination. The patient was a well nourished middle-aged man who appeared moderately ill and who lay on his right side to relieve his pain. Complexion sallow and conjunctivae pale, but no definite icterus demonstrable. Temperature 101° F., pulse 80, respirations 20. Eyes, ears, nose and throat normal. Trachea in mid-line. Thyroid normal. Chest symmetrical, expansion equal on both sides. Compression of right lower chest caused considerable pain. Lungs clear. Heart normal. No signs of elevated diaphragm by percussion, but both bases descended poorly on inspiration. Blood pressure 125 mm. Hg systolic and 65 mm. diastolic. Abdomen soft, flat, symmetrical. Moderately firm, exquisitely tender liver edge palpated four fingers' breadth below the right costal margin. Anterior surface of the liver definitely convex. Spleen not felt. Genitalia normal. No hernia. Extremities normal. No ankle edema. Reflexes in order. No enlarged lymph nodes.

Laboratory Findings. Red blood cells 4,750,000. Hemoglobin 90 per cent. White blood cells 16,150. Differential smear: polymorphonuclears 86 per cent (11 stabs, 75 segs.), eosinophiles 1 per cent, lymphocytes 11 per cent, monocytes 2 per cent. Urinalysis: dark amber, hazy, acid specific gravity 1.024, albumin 2 plus, sugar negative. Microscopic: few epithelial cells. Routine stool: precystic forms of *E. histolytica*. A second specimen examined on September 30 revealed actively motile vegetative forms of *E. histolytica*. Kahn negative. Sedimentation rate: 58 mm. in one hour (Wintrobe).

Roentgen Studies. September 4: chest roentgenogram negative, except for slightly elevated left diaphragm due to distended colon. Abdominal roentgenogram showed downward enlargement of liver, 4.5 cm. below the costal margin, and marked distention of the splenic flexure and descending colon. September 29: chest roentgenogram negative. Roentgenogram of abdomen showed increased downward enlargement of the liver, 6 cm. below the right costal margin.

Course. A clinical diagnosis of amebic abscess of the liver was made on admission and emetine therapy was started, one grain intramuscularly daily. For the first few days the patient's condition appeared to get worse. He ran a high remittent fever, ranging between 101° and 103.5°, the abdominal pain increased and interfered with sleep, the convexity of the anterior surface of the liver increased, giving rise to a poorly defined dome-shaped mass beneath the right upper rectus muscle, and he developed a dry irritative cough.

The first sign of improvement was a definite fall in temperature on the fifth day of emetine therapy. Liver pain and enlargement began to subside three days later. The temperature was normal by the fourteenth day, liver pain and tenderness were gone by the twenty-first day and the liver had receded to the costal margin by the fifty-first day.

The first course of treatment consisted of 10 grains of emetine. After an interval of three days, three more grains were given because fever and pain persisted. The temperature fell to normal and the pain subsided. Two more courses of emetine, 6 grains each, were required at 10- and six-day intervals because of recrudescences of fever and pain. In all, the patient received 25 grains of emetine over a period of 43 days.

Concomitant with the last two courses of emetine the patient received both

carbarsone and chiniofon. Check stools at the end of treatment were negative for *E. histolytica*.

The white blood count gradually fell as the liver receded and was normal by the twenty-second day. The sedimentation rate, however, remained elevated long after hepatic tenderness was no longer demonstrable and did not reach normal until the fifty-ninth day.

During the first three weeks of his illness, the patient lost considerable weight. His appetite returned to normal when he was afebrile and his weight gradually returned to its previous level.

On discharge from the hospital on the sixtieth day, the patient felt perfectly well and he was returned to full military duty. His liver edge was still palpable at the costal margin, but it was no longer tender and there was no compression tenderness of the right lower chest.

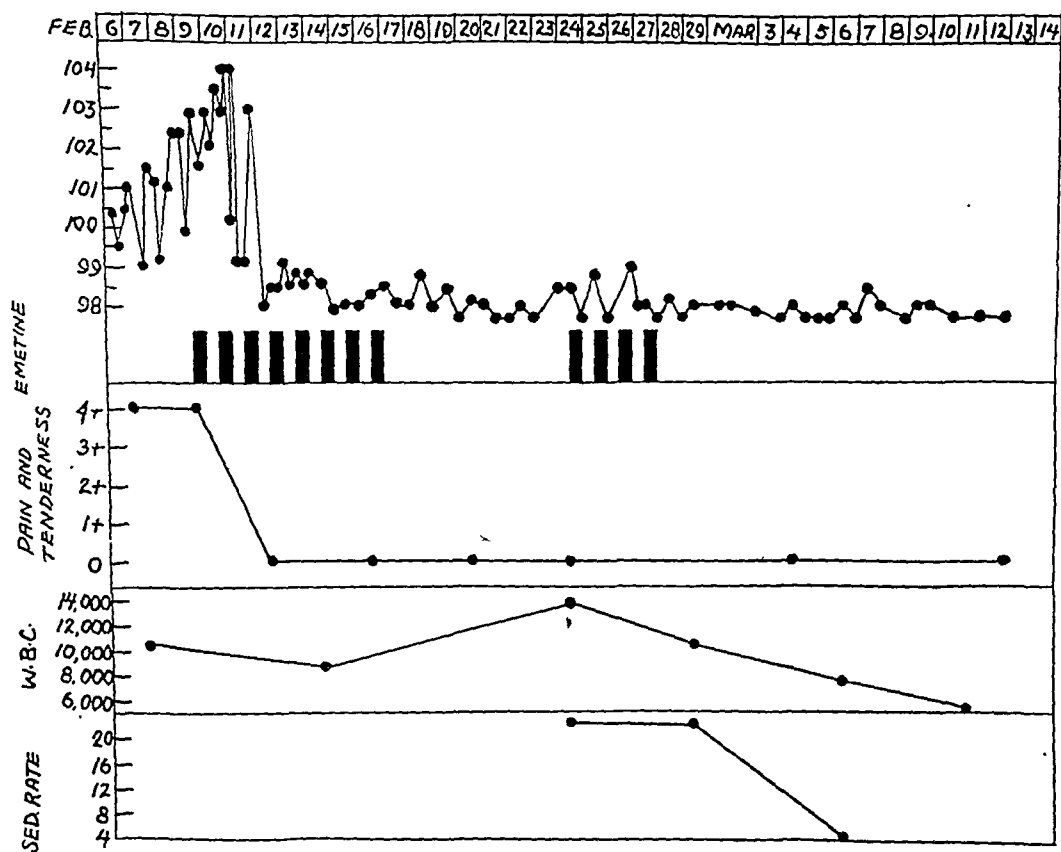


FIG. 2. Case 2. Acute amebic hepatitis.

Case 2. Acute Amebic Hepatitis (Figure 2).

History. A 27-year old colored soldier was admitted to the hospital on February 6, 1943, with the history of a sudden onset of severe sharp pain in the right lumbar region, right shoulder and right side of the neck two days before admission. The next day he had developed a head cold and cough productive of a small amount of mucus.

The patient had been in India for 21 months. Four months after his arrival, he had contracted amebic dysentery for which he had received what is said to have been adequate treatment. Since then he had had no gastrointestinal symptoms. He drank very little alcohol. His past history was otherwise non-contributory.

Examination. The patient was well developed and well nourished and did not appear ill. Temperature 100, pulse 84, respirations 21. Nasal and pharyngeal mucosa inflamed. Slight splinting of right side of chest with suppression of the breath sounds at the right base. No impairment of resonance or râles. No friction rub heard. Heart normal. Abdomen normal except for tenderness on deep palpation beneath the right costal margin. Liver not felt.

Laboratory Findings. White blood cells 10,330. Differential count: polymorphonuclears 74 per cent, lymphocytes 26 per cent. Urinalysis: amber, clear, acid, specific gravity 1.021, albumin negative, sugar negative; microscopic: occasional mucous threads and calcium oxalate crystals. Kahn reaction doubtful on first test, negative on second test. Sedimentation rate: 22 mm. in one hour. Two routine stools negative for *E. histolytica*.

Röntgenographic Studies. Chest negative.

Course. The admission diagnosis was: (1) Nasopharyngitis, (2) pleurisy or amebic abscess of the liver. The temperature gradually rose in step-like fashion reaching a maximum of 104° on the fourth day. The pulse rate was proportionally increased and the respiratory rate ran between 24 and 26. There were several shaking chills.

The day after admission the patient localized his pain in the right lower chest and anterior-posterior compression was found to cause considerable pain. It continued to radiate to the right shoulder and the right side of the neck, especially on deep inspiration. At no time could the liver be felt.

In view of the negative chest film, the high fever, the leukocytosis, the compression tenderness of the right lower chest and the history of amebic dysentery in the past, a diagnosis of acute amebic hepatitis was made and emetine therapy started, one grain daily.

There was a marked drop in temperature and the pain and compression tenderness disappeared after the third dose of emetine. The temperature reached normal and remained so after five grains of emetine. The white blood cell count and the sedimentation rate remained elevated for some time and returned to normal 28 days after emetine had been started.

The first course of emetine consisted of 8 grains. After an interval of seven days, a second course of 4 grains was given. The latter was supplemented with a course of chiniofon. A check stool at the end of treatment was negative for *E. histolytica*.

The patient was discharged on the thirty-sixth day at which time he felt perfectly well. Abdominal and chest examination was entirely normal and he was returned to full duty.

Case 3. Subacute Amebic Hepatitis.

History. A 25-year old officer with 13 months' service in India, was admitted to the hospital on October 30, 1944 complaining of intermittent watery diarrhea, and abdominal pain.

Ever since his arrival in India the patient had had frequent attacks of watery diarrhea lasting two to three days. These had subsided spontaneously or following the administration of sulfaguanidine. In February 1944, a single stool specimen had been examined and found to be free of *E. histolytica*. His last attack of diarrhea had started three days before admission.

For the two weeks preceding admission, the patient had been troubled with abdominal pain. At first the pain had been located in the lower abdomen and had been aggravated by physical exercise and relieved by defecation. Later, it had shifted to the right upper quadrant beneath the costal margin and was described as sharp and intermittent. It did not radiate and was unaffected by deep breathing, lying on the side, twisting, bending or jarring.

There had been no fever, chills or other constitutional symptoms. Past history was non-contributory.

Examination. The patient lay in bed without apparent discomfort and did not appear ill. Skin normal, no icterus. Eyes, ears, nose, throat normal. Lungs clear on auscultation and percussion. Heart normal. Moderate anterior-posterior and mild lateral compression tenderness of the right lower chest. Abdomen soft with tenderness beneath the right costal margin, and to a lesser degree in the left lower quadrant and peri-umbilical region. On the first examination the liver could not be felt. Two days later it was easily palpable two fingers' breadth below the costal margin and was found to be soft and moderately tender. Remainder of examination normal.

Laboratory Findings. White blood cells 5,500. Differential smear: polymorphonuclears 79 per cent, lymphocytes 14 per cent, monocytes 6 per cent, eosinophiles 1 per cent. Sedimentation rate: 14 mm. in one hour. Stool positive for *E. histolytica*.

Course. Emetine therapy, one grain daily, was started as soon as *E. histolytica* was demonstrated. Liver pain and tenderness began to subside on the third day and were absent on the fourteenth day of treatment. The liver edge receded rapidly, but was still palpable at the costal margin on the fifteenth day when the patient was discharged to duty. However, it was no longer tender and there was no compression tenderness over the lower right chest. The sedimentation rate was normal on the fourteenth day.

The patient received a total of 12 grains of emetine over a 15-day period. He was also given a seven-day course of Diodoquin 0.63 gm. t.i.d., followed by a seven-day course of carbarsone, 0.25 gm. t.i.d. At the end of this treatment, three stools were examined following the administration of a large dose of magnesium sulfate and no *E. histolytica* could be demonstrated. There was no diarrhea or pain and the patient felt perfectly well.

He was discharged to full military duty on the fifteenth hospital day.

Case 4. Chronic Amebic Hepatitis.

History. A 37-year old soldier with 20 months' service in India was admitted to the hospital on November 30, 1944 complaining of pain in his upper abdomen.

For one year he had experienced pain in the right upper quadrant. The pain was sharp in character, moderately severe and was brought on by jarring, such as occurred while riding in a truck over rough roads, by deep breathing and by twisting or turning suddenly. It frequently occurred at night while he lay on his back and it was relieved by lying on either side. At times it radiated to the right lumbar region.

There was no relationship between the pain and the ingestion of food and the patient denied indigestion, diarrhea, cramps, intolerance for fatty foods and jaundice in the past. At times he had noted nausea, but never any vomiting.

There were no cardio-respiratory or genito-urinary symptoms. The past history was non-contributory.

Examination. The patient was a husky man of 37 who did not appear ill. Skin was normal, no icterus or pallor. There was moderate dental caries. Nose and throat were normal. Chest was symmetrical. Anterior-posterior and lateral compression of the right lower chest caused pain. Lungs were normal on percussion and auscultation. There was marked tenderness without spasm beneath the right costal margin. The liver by percussion was two fingers' breadth below the costal margin, but its lower edge could not be palpated owing to a thick abdominal wall. The next day it was easily palpable one finger's breadth below the costal margin and it was found to be moderately tender. Kidneys and spleen were not felt. Extremities were normal. Reflexes were physiological.

Laboratory Findings. Red blood cells 4,890,000. Hemoglobin 90 per cent. White blood cells 11,900. Sedimentation rate: 21 mm. in one hour. Urine: straw

color, clear, acid, specific gravity 1.017, albumin negative, sugar negative. Stool examination, after one ounce of magnesium sulfate, revealed actively motile trophozoites of *E. histolytica*.

Roentgenographic Studies. Cholecystogram after oral dye showed normal filling and emptying of the gall-bladder. No biliary calculi were demonstrated.

Course. Emetine therapy, 1 grain daily, was started the day after admission. Pain and liver tenderness were definitely diminished on the fourth and absent on the twelfth day of therapy. The liver was no longer palpable and compression tenderness of the right lower chest was absent on the sixth day. The sedimentation rate had dropped to 10 mm. in one hour by the tenth day. A total of 12 grains of emetine was given over a 15-day period. The entire course was afebrile except for rises to 99 on two occasions.

The emetine therapy was supplemented with a course of Diodoquin, 0.63 t.i.d. for seven days and a course of carbarsone, 0.25 gm. t.i.d. for seven days. Check stools, after a dose of magnesium sulfate, were negative for *E. histolytica*.

The patient was discharged on the nineteenth hospital day and returned to full military duty.

PREDISPOSING FACTORS

Alcohol. The rôle of alcohol as a predisposing factor in the development of hepatic amebiasis has been a matter of controversy.^{1,7} In the present series no relationship could be demonstrated between the two. Of the 62 cases, 23 were total abstainers, 18 drank very little and 21 drank moderately.

Age. The average age was 29.8 years, considerably higher than the average for all admissions to the hospital. Thirty-three patients were between the ages of 20 and 29, 24 between 30 and 39, and five between 40 and 49. The youngest patient was 20 and the oldest 47. In general these findings confirm the consensus of opinion that the disease occurs chiefly between 30 and 50 and that it is rare below the age of 20 or above 50.^{1,7}

Sex. No sex preponderance could be demonstrated when the relative admission rates for males and females were taken into account. Two of our 62 cases were female—an incidence of 3.2 per cent which was slightly higher than the average admission rate for females. Other observers^{1,13} have noted a much greater susceptibility of males to the disease.

Race. Natives in the tropics are said to show a much lower incidence of hepatic amebiasis than Europeans.¹ This is difficult to explain since the former almost certainly have a higher colonic infection rate. A recent study by Payne³ casts considerable doubt on the concept of racial immunity. No such immunity has been demonstrated in the negro and our findings confirm this. Six of our 62 cases were negroes—an incidence of 9.7 per cent which was a little higher than the average negro admission rate.

Trauma. In some instances trauma has precipitated the development of an amebic abscess of the liver.⁷ There was no history of trauma to the liver in any of our cases.

Amebic Dysentery. Only eight of our cases (13 per cent) gave a definite history of amebic dysentery in the past, but 39 (63 per cent) had a history of intermittent diarrhea suggesting amebiasis.

The interval between the attack of dysentery and the onset of hepatic amebiasis averaged 7.3 months. The shortest interval was two weeks, the longest 17 months.

In those with a history of intermittent diarrhea it had been present on an average of 5.6 months (one week to 20 months).

Although a history of antecedent amebic dysentery is often lacking, there is good evidence to support the view that hepatic amebiasis is invariably preceded by amebic ulceration of the colon. Many of the latter are asymptomatic and some have healed by the time liver disease becomes apparent clinically. In Rogers' series of amebic abscess cases coming to autopsy, 77.8 per cent had evidence of active dysentery and 20 per cent demonstrated the scars of healed dysentery.¹¹

Residence in the Tropics. The average residence in the tropics before the development of symptoms was 11.8 months. The shortest was six weeks, the longest two years. Most of the patients had served in India only, but there were a few who had also served for varying periods in China, Iran and North Africa.

SYMPTOMS

Onset. In general, the onset of symptoms was sudden in abscess and acute hepatitis and gradual in subacute and chronic hepatitis. The duration of symptoms before admission to the hospital averaged less than 10 days in abscess, acute and subacute hepatitis, and averaged 5.7 months in chronic hepatitis (table 1).

TABLE I
Onset and Duration of Symptoms before Admission to the Hospital

	Onset		Duration	
	Sudden	Gradual	Average	Range
Acute abscess	5 cases	2 cases	5.4 days	3-8 days
Acute hepatitis	10	6	3.4 days	1-10 days
Subacute hepatitis	10	22	8.7 days	2-30 days
Chronic hepatitis	0	7	5.7 mos.	2-12 mos.

The initial symptoms were quite variable, but generally, in the course of a few days others developed which clearly indicated the nature of the disease. The abscess and acute hepatitis cases usually came to the hospital because of fever and liver pain, but a few had only fever, cough, chest pain or diarrhea. Onset with liver pain was much less common in subacute hepatitis, and fever was rarely an initial complaint. Many of these patients started with diarrhea and cramps and only later developed liver pain. Several were actually under treatment for amebic dysentery when symptoms of hepatic involvement appeared. All the patients with chronic hepatitis came to the hospital because of liver pain. In a few the pain had been preceded

or accompanied by diarrhea, but the latter was never the cause for admission and was usually considered insignificant.

Liver Pain. Liver pain was by far the most common symptom in all forms of hepatic amebiasis. It occurred in all the abscess and chronic hepatitis, in most of the acute and in about half of the subacute hepatitis cases (figure 3).

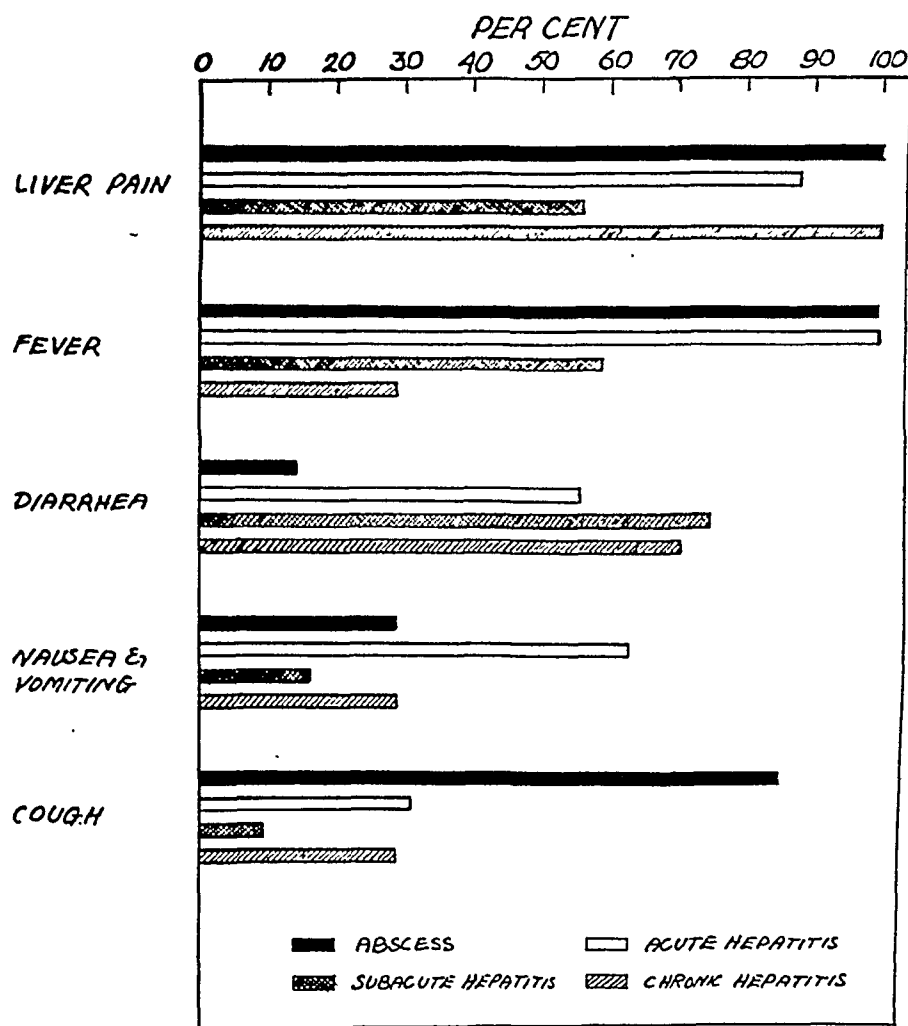


FIG. 3. Principal symptoms of hepatic amebiasis.

The pain had a number of distinctive features, which, when carefully analyzed, usually indicated the liver and excluded other structures above and below the diaphragm as the source of the pain. These features were its location, character, severity, radiation and aggravation by movements and change in position (figure 4).

Liver pain was usually localized in the right upper quadrant of the abdomen beneath the costal margin. Characteristically many of the patients indicated its location with the fingers cupped and resting just below the right

costal margin. It was localized less commonly in the epigastrium and in the right lower chest.

In three cases (one abscess, one acute hepatitis and one chronic hepatitis), the pain was localized in the left upper quadrant, and the clinical evidence indicated primary involvement of the left lobe of the liver. Although the right lobe is usually involved, a number of left sided amebic abscesses have been recorded.

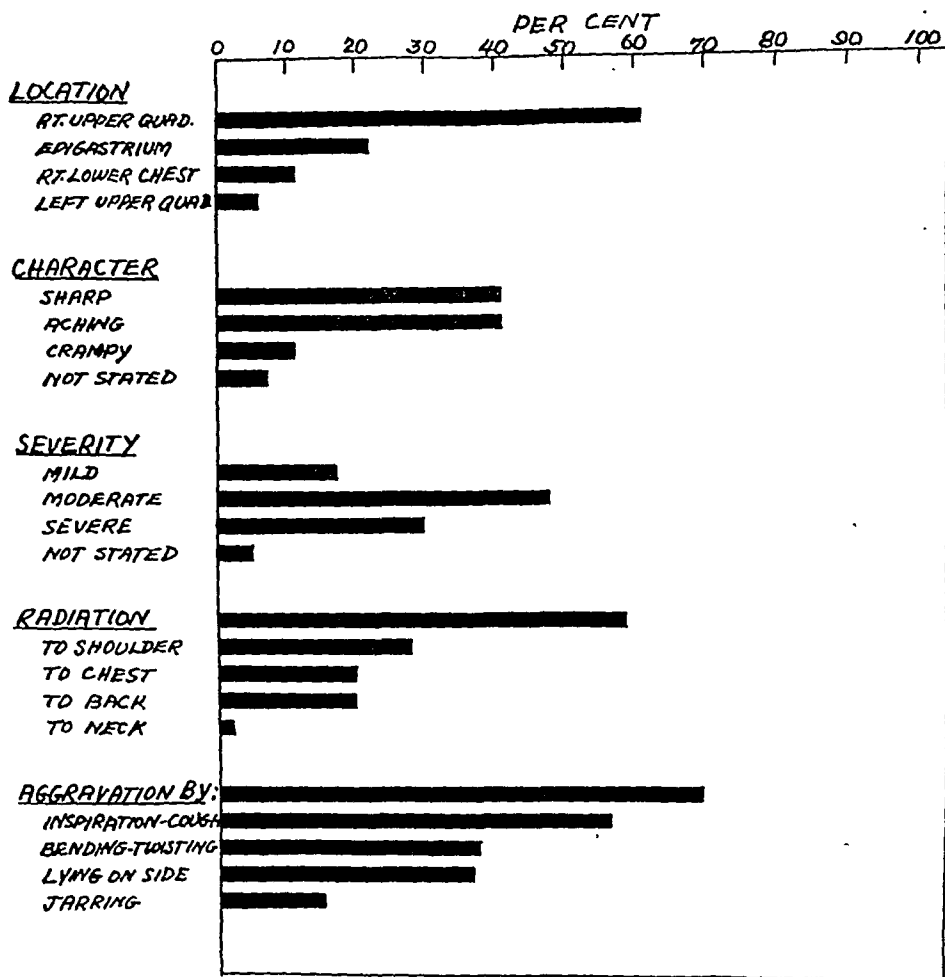


FIG. 4. Characteristics of liver pain in 46 cases of hepatic amebiasis.

As a rule it was described as a constant ache, or an intermittent sharp pain, usually brought on by characteristic movements or change in position. Although a few patients described it as crampy, it was never colicky, as in ureteral or biliary colic.

For the most part the pain was only moderate in severity. Most of the cases with severe pain fell into the abscess and acute hepatitis groups. Only three patients with subacute hepatitis had severe pain.

Aggravation of the pain by movements and change in position was a prominent feature and was of great diagnostic significance. The principal

aggravating factors were deep breathing and cough, bending and twisting, lying on either side and jarring. Frequently the patient spontaneously offered the information that these produced or aggravated his pain, but in many instances it was necessary to inquire specifically about their effect. The effect of jarring, especially on riding over rough terrain, probably occurred more frequently than indicated, as many of our patients were not asked about it.

Radiation of the pain was very common, especially on movement or change in position. In several instances the first complaint was pain at the site of radiation, and only later was pain noted in the liver. This led to a number of diagnostic errors, especially when radiation to the chest occurred. The common sites of radiation were the shoulder, chest and lumbar region. On one occasion it radiated to the neck. Radiation was always to the right, except in the three patients with involvement of the left lobe of the liver in whom radiation occurred to the left.

Fever. All the abscess and acute hepatitis, but only half of the subacute and a third of the chronic hepatitis cases had fever (figure 3). There were striking differences between the fever of the abscess and acute hepatitis groups on the one hand and the subacute and chronic hepatitis groups on the other. In the former it was always high and usually remittent or continuous, whereas in the latter it was low-grade and usually intermittent (table 2).

TABLE II
Characteristics of Fever Exhibited in Hepatic Amebiasis

	Patients	With Fever	Height of Fever		Type of Fever			Chills	Sweats	Brady- cardia
			Average Maximum	Range	Contin- uous	Remit- tent	Inter- mittent			
Abscess	7	7	103.4	102.5-104	1	6	0	5	4	5
Acute hepatitis	16	16	103.4	101.5-105	2	11	3	10	6	9
Subacute hep- atitis	32	19	100.3	99.5-102	0	2	17	1	0	0
Chronic hepatitis	7	2	100.9	99.5-102.3	0	0	2	1	0	1

There were only two cases of subacute hepatitis with a fever over 101° and in both instances it was very irregular and intermittent. One case of chronic hepatitis, with a history of liver pain for three months, had an intermittent fever up to 102.3 for eight days. It was felt he was entering the acute phase of the disease.

Chills and, to a lesser extent, sweats were common in both the abscess and acute hepatitis groups. Relative bradycardia and high fever, with pulse rates between 70 and 80, were also seen frequently in abscess and acute hepatitis (table 2).

In several instances fever preceded the onset of liver pain and tenderness and the patients were thought to have one of the infectious diseases on ad-

mission to the hospital. The temperature-pulse curves in the three cases with continuous fever resembled those seen in typhoid fever.

Diarrhea. The absence of symptomatic dysentery in many abscesses of the liver has been noted by others,^{1, 7} and Rogers⁸ has suggested that this is due to the predominance of amebic ulcerations in the cecum and ascending colon. Diarrhea occurred but once in our abscess group, but was very common in the other groups (figure 3).

None of the cases with diarrhea had gross blood or mucus in the stools. As a rule the diarrhea was mild and the stools were mushy or watery.

Abdominal cramps, chiefly in the lower quadrant but occasionally generalized, accompanied the diarrhea in only one-third of the cases and occurred almost exclusively in the subacute hepatitis group. This was the group, it will be recalled, in which diarrhea was a frequent primary complaint. In two instances abdominal cramps occurred without diarrhea. There was rarely any difficulty in differentiating liver pain from cramps due to associated dysentery.

Nausea and Vomiting. Either or both occurred in about a third of the cases and were most common in the acute hepatitis group (figure 3).

The nausea and vomiting promptly subsided with the institution of emetine therapy and were rarely associated with anything but transient anorexia or indigestion, two points of considerable importance in differentiating this disease from infectious hepatitis.

Cough. Cough was an important symptom, especially in the abscess group although it also occurred to a lesser extent in the other groups (figure 3).

Of the 16 patients with cough, seven had chest pain. There were also nine cases of chest pain without cough. The pain in both instances was undoubtedly hepatic in origin. Nevertheless, it focused attention on the lungs, as did the cough, and led to diagnostic errors. Chest pain was the initial symptom in eight cases and was associated with cough in seven and fever in five.

As a rule the cough was dry and irritative, but in one-third of the cases it was productive of sputum.

PHYSICAL FINDINGS

General Appearance. The patients with abscess and acute hepatitis usually appeared acutely or moderately ill, while those with subacute and chronic hepatitis appeared mildly ill or not ill at all (table 3).

A few patients showed evidence of recent *weight loss*, but it was never marked. It is apparently a much more frequent finding in chronic amebic abscess.

The *sallow complexion* said to be characteristic of hepatic amebiasis was seen in only five patients—one acute abscess, three acute hepatitis and one chronic hepatitis. It too probably occurs principally in the chronic abscess group.¹

TABLE III
Apparent Severity of Illness on Examination

	Acute	Moderate	Mild	Not ill
Abscess	3	2	1	1
Acute hepatitis	6	3	2	5
Subacute hepatitis	0	2	0	28
Chronic hepatitis	0	0	1	6

Clinical *jaundice* was not seen in any of our patients, although the icteric index was 19 in one and traces of bile were found in the urines of five. Frank jaundice has been reported in 10 to 30 per cent of patients with hepatic amebiasis,^{1, 13} but Brown and Hodgson¹³ report that it is never intense. It would appear from the cases reported that jaundice also occurs chiefly in the chronic abscess group.

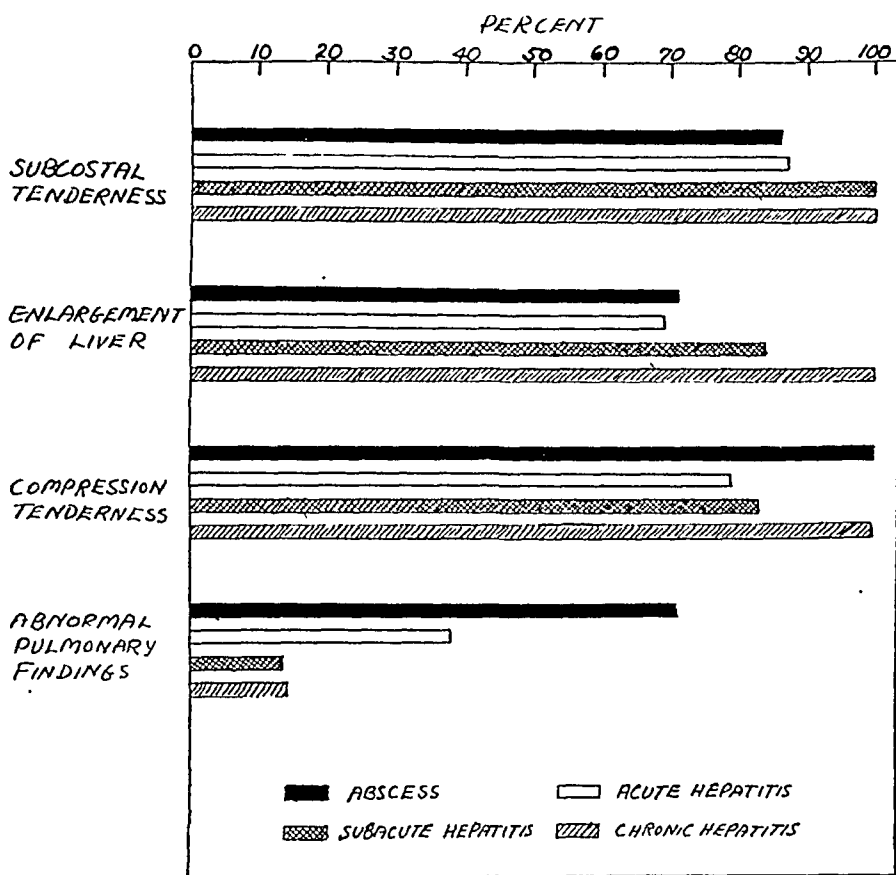


FIG. 5. Principal physical findings in hepatic amebiasis.

Abdominal Findings. Subcostal tenderness was the most frequent abnormality noted (figure 5). It occurred in all the subacute and chronic hepatitis and in most of the other cases. It was associated with spasm of the upper right rectus muscle in eight patients.

Palpable enlargement of the liver was easily demonstrable in most of the patients, but it was absent in two with abscess, five with acute hepatitis and five with subacute hepatitis (figure 5). The enlargement varied from one to four fingers'-breadth below the right costal margin. In two of the three cases with left lobe involvement, the right lobe was also enlarged. The liver edge was usually soft and sharp and was always tender. Tenderness varied considerably from case to case, but was, in general, most severe in abscess and acute hepatitis. Subcostal tenderness frequently preceded palpable enlargement by several days.

A definite visible and palpable bulge of the liver was demonstrable in six of the seven abscess cases. In the seventh it was demonstrable by roentgen-ray only. It was located in the epigastrium in three, beneath the right lower ribs in two and beneath the left costal margin in one. The swelling was usually doughy and invariably exquisitely tender. Fluctuation was never demonstrated. The overlying skin showed no changes, but in one case, involving the left lobe, the overlying abdominal wall seemed edematous and tender and attached to the underlying mass.

Upward enlargement of the liver was demonstrated by percussion in three and by roentgen-ray in eight cases.

Compression tenderness of the liver was a finding of considerable importance and was present in 43 of the 50 cases tested. It was demonstrated in all the abscess and chronic hepatitis and in most of the acute and subacute hepatitis cases tested (figure 5). Tenderness was elicited by compressing the lower right chest anterior-posteriorly between the palms of the hands. The test was considered positive only when the patient complained of moderate to severe pain. As a rule subjective pain was associated with wincing. Mild pain or a feeling of pressure was not considered significant. Except when anterior-posterior tenderness was severe, lateral compression tenderness was usually not demonstrated. In the three cases of left lobe involvement, compression tenderness was demonstrated on the left, and in one, it was present on both sides.

The compression test proved to be of great help in differential diagnosis. It clearly demonstrated the hepatic origin of the pain and differentiated it from that arising in other structures above and below the diaphragm. The test was tried in a great variety of conditions including pneumonia, pleurisy, renal colic, pyelitis, acute dysentery, peptic ulcer and malaria with enlargement of the liver and was invariably negative. It was also of some value in differentiating amebic from infectious hepatitis. In a large series of infectious hepatitis cases, in which the test was tried, it was negative in all but a few. The only other condition in which the test was invariably positive was acute cholecystitis. No doubt there are other conditions, such as subphrenic abscess, in which the test may be positive.

Compression tenderness is by no means to be considered pathognomonic of hepatic amebiasis, but it has proved its worth as a confirmatory finding, and in a few instances it has made an early diagnosis possible in the absence

of other findings. In five cases, one abscess, two acute hepatitis and two subacute hepatitis, it was the only physical finding other than fever on admission to the hospital. Subsequently in three of them liver enlargement and subcostal tenderness became apparent. The compression test has been found valuable by others,¹³ but it has never received the emphasis it deserves.

Of the 62 cases, 61 showed one or more of the three principal physical findings—compression tenderness, subcostal tenderness and palpable liver enlargement (table 4). The last case came to the hospital with severe right

TABLE IV
Principal Abdominal Findings

	Early*	Late
Compression tenderness alone†	5	2
Subcostal tenderness alone	1	0
Liver enlargement alone	0	0
Combination of any two signs	29	26
Combination of all three signs	25	33
No signs	2	1

* On admission to the hospital.

† Tested in 50 cases.

subcostal pain, aggravated by breathing, movement and lying on the left side, and a remittent fever up to 104°. Physical examination was entirely negative except for a few râles at the left base. The white blood cell count was 13,650 with 69 per cent polymorphonuclears. A routine stool was negative for *E. histolytica*, and a roentgen-ray of the chest was normal. On emetine therapy there was a prompt clinical response, with subsidence of pain, fever and leukocytosis.

Percussion tenderness over the liver has been stressed by some,¹⁴ and it was found to be present in a few of the cases in which it was tested.

Only one of our patients had a localized area of tenderness in the intercostal spaces, a sign said to be of some merit in the diagnosis of amebic abscess.

Many of the patients with associated dysentery had mild tenderness along the course of the colon, especially in the right lower quadrant. The cecum was occasionally thickened and tender.

The spleen was palpable in only one patient. Since he had lived in a malarious area for some time, it was considered unrelated to the liver disease.

Pulmonary Findings. Abnormal physical findings were noted in the chest in 26 per cent of our patients. They were common in the abscess group, but also occurred to a lesser extent in the others (figure 5). The abnormalities were always in the right lower lobe, except in the three cases of left sided hepatic amebiasis.

The physical signs were definite, although never marked, and usually suggested early pneumonia (table 5).

ROENTGEN-RAY FINDINGS

Chest. Roentgen-ray examination of the chest was performed in 36 patients and abnormalities were noted in 17. As in the case of cough and

TABLE V

Abnormal Pulmonary Physical Findings Found in 16 Patients with Hepatic Amebiasis

Increased respiratory rate (over 25 per min.)	16
Suppressed breath sounds	11
Dullness on percussion	5
Râles	5
Splinting of the lower chest	5

abnormal chest findings on physical examination, they were most common in the abscess and acute hepatitis groups (table 6).

TABLE VI

Chest Roentgen-Ray Findings in Hepatic Amebiasis

	Abscess	Acute Hepatitis	Subacute Hepatitis	Chronic Hepatitis	Total
Number of patients examined	7	12	13	4	36
Number with abnormal findings	5	7	4	1	17
Diaphragm					
Elevation	3	4	1	0	8
Flattening	2	0	1	0	3
Obliteration of C.H.†	0	1	0	1	2
Limited motion*	0	1	0	0	1
Local bulge	1	0	0	0	1
Lungs					
Increased markings	2	5	3	1	11
Haziness	1	0	0	0	1
Effusion (slight)	0	0	1	0	1

* Number of fluoroscopic examinations not known.

† C.H. = cardiohepatic angle.

When abnormalities were noted in the lungs they were usually interpreted as probable early pneumonia, and the roentgenologist frequently recommended a second roentgen examination in 24 to 48 hours. This was especially true when the clinical history was not submitted with the request for roentgen-ray examination. When the clinical diagnosis of hepatic amebiasis was suggested or when the diaphragm was elevated, the roentgenologist frequently confirmed the diagnosis. In brief then, the findings in most cases were not sufficiently characteristic to warrant a diagnosis of hepatic amebiasis. Unfortunately fluoroscopy was not done routinely so that the question of diaphragmatic movement was not investigated in every case.

Of the 15 patients with involvement of the right lobe of the liver who exhibited abnormalities in the chest roentgen-ray, 14 had them at the right base and in the right leaf of the diaphragm, and one had lung changes at both bases. Of the two patients with involvement of the left lobe of the liver with roentgenographic abnormalities, one had them on the left, the other bilaterally.

It seemed probable to us that the pulmonary changes found were due to a mild degree of atelectasis, secondary to splinting of the chest, to pressure of the liver from below and to partial or total restriction of the right hemidiaphragm. The elevation and immobility of the diaphragm are thought to

be due to inflammation and edema by direct extension from the underlying inflamed liver.¹⁵ It is not surprising, therefore, to find so few changes in the diaphragm in the present report, since most of the cases were seen very early and since in only one of the cases was it possible to demonstrate an abscess in the dome of the liver. Munk¹⁶ has stressed the fact that signs in the diaphragm are lacking where the enlargement of the liver is chiefly anterior and inferior.

In more advanced cases, and particularly with abscesses located close to the dome of the liver, one frequently finds pleurisy, pleural effusion and true pneumonitis.^{7, 16} These cases also usually exhibit roentgen findings which are considered diagnostic of liver abscess—namely, elevation, fixation and local bulging of the diaphragm, obliteration of the cardiohepatic angle in the postero-anterior view and obliteration of the anterior costophrenic angle in the lateral view. Subphrenic abscess due to other causes, on the other hand, gives a similar picture, but the costophrenic angle is obliterated laterally in the postero-anterior view and posteriorly in the lateral view.¹

Only one of our cases had a mild pleural effusion and none had pneumonitis. The other roentgen-ray findings generally considered characteristic of amebic abscess were relatively infrequent, and when present were usually minimal in degree (table 6).

Very bizarre roentgen findings may be demonstrated when a liver abscess ruptures into the pleural space or lung, resulting in empyema, lung abscess or bronchohepatic fistula, with or without accompanying pneumonitis. Occasionally amebic abscess of the lung complicates abscess of the liver without any apparent anatomic connection between the two. No such cases were seen in this group.

Abdomen. Enlargement of the liver was demonstrated in only four of the 15 patients who had antero-posterior films of the abdomen, yet 14 of them had enlarged tender livers on palpation. It would appear that the determination of liver size by roentgen examination in this disease is of little value.

Gall-Bladder. Six patients with subacute and chronic hepatitis were subjected to cholecystography. The gall-bladder proved to be normal in every instance.

LABORATORY FINDINGS

Blood Count. All of the abscess, 75 per cent of the acute, and a few of the subacute and chronic hepatitis cases exhibited leukocytosis. It was most marked in the abscess group (figure 6, table 7). Two patients with acute hepatitis had leukopenia on admission, but one of them subsequently developed leukocytosis. Chronic amebic abscess is also occasionally associated with a normal white blood cell count.¹

The percentage of polymorphonuclear cells was usually only slightly elevated, an important point in differential diagnosis first noted by Rogers.⁸ It was highest in the abscess group (table 7). Only one patient had a count

as high as 90 per cent. It may rise to very high levels when secondary bacterial infection occurs in an amebic abscess.

Secondary anemia is said to occur frequently in the more chronic forms of amebic abscess.¹ None was demonstrated in any of our cases.

Sedimentation Rate. An elevated sedimentation rate was found in all the abscess cases and in a high proportion of the others tested. In general it was the highest in the abscess and lowest in the chronic hepatitis group (table 7). The test was not nearly as important in diagnosis as it was in following the course of the disease under treatment.

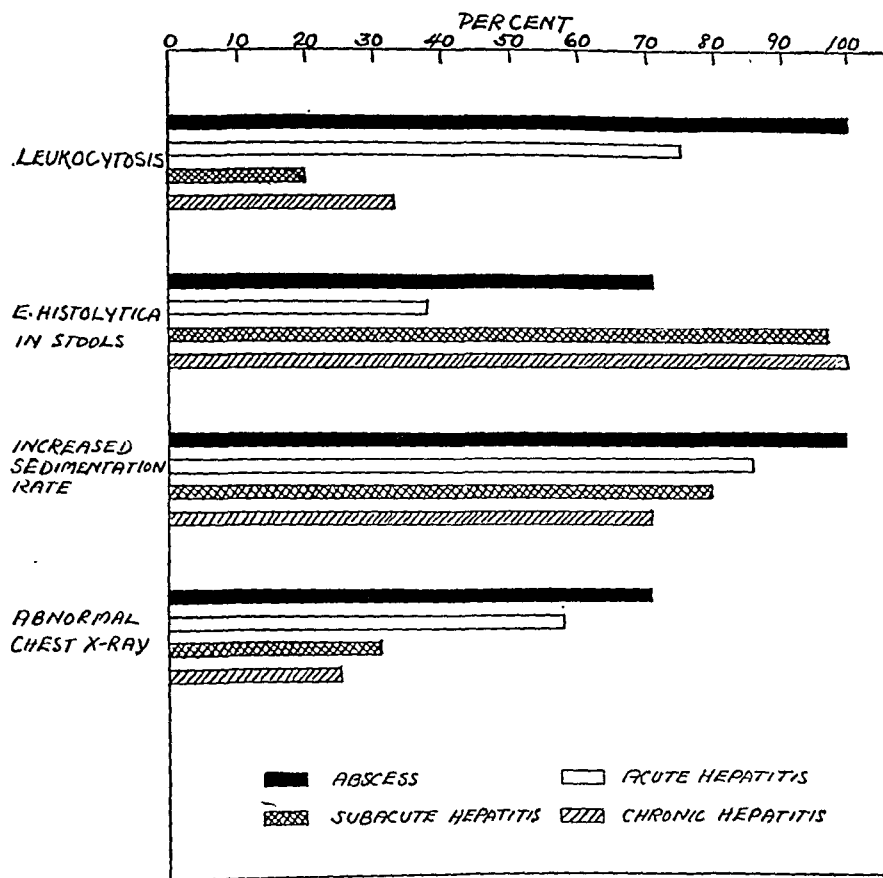


FIG. 6. Principal laboratory and roentgen-ray findings in hepatic amebiasis.

Stool Examination. *E. histolytica* were demonstrated in the stools of 80 per cent of the entire group. They were found in all the chronic and most of the subacute hepatitis groups, but were frequently absent in the acute hepatitis and abscess groups (figure 6, table 7). Others¹ have found the stools negative in an even higher proportion of abscess cases.

In almost every instance where the stool was positive, the characteristic actively motile trophozoites of *E. histolytica* were demonstrated.

Later experience convinced us that a much higher proportion of positive stools could be obtained by examining them following a strong saline purge.

TABLE VII
Summary of Laboratory Findings

	Abscess	Acute Hepatitis	Subacute Hepatitis	Chronic Hepatitis	Total
White blood cell count					
Cases tested	7	16	30	6	59
W.B.C. over 10,000	7	12	6	2	27
Range	11,200- 22,000	3,400- 16,700	4,500- 16,650	6,000- 15,750	
Average	15,964	12,215	8,156	9,636	
Polymorphonuclears					
Range (per cent)	71-90	40-85	47-85	57-74	
Average (per cent)	83	72	67	66	
Sedimentation rate*					
Cases tested	4	7	25	7	43
Above 10 mm./hr.	4	6	20	5	35
Range (mm./hr.)	27-70	3-67	3-49	5-40	
Average (mm./hr.)	53	26	23	17	
Stools					
Cases tested	7	16	32	7	62
<i>E. histolytica</i> present	5	6	31	7	49
Albuminuria					
Cases tested	7	14	21	6	48
Number positive	3	1	0	0	4
Bile in urine					
Cases tested	0	5	7	2	14
Number positive	—	3	2	0	5
Increased urobilinogen					
Cases tested	0	4	1	1	6
Number positive	—	3	1	1	5

* Wintrobe method.

Others have made the same observation.⁷ Of the 37 patients, whose normally passed stools were examined, only 24 (60 per cent) were positive, whereas all of the 25 cases examined after a purge were positive. Our technic was quite simple and consisted of examining wet smears from the second, fourth and sixth stools passed after the administration of one ounce of magnesium sulfate crystals in a glass of water. Occasional patients required a larger dose. If the first series of stools was negative, a second series was examined after a two or three day interval. In a few instances the latter were positive. Iodine-stained wet preparations were examined for cysts only when trophozoites were not found. In only one instance were cysts of *E. histolytica* demonstrated.

Urine. Albuminuria was found in four of the patients with high fever and was considered of no significance since it promptly disappeared when the fever subsided.

Traces of bile were demonstrated in five of the 14 cases tested, but in every instance the icteric index was normal.

Increased urobilinogen was demonstrated in five of the six cases tested.

Liver Function Tests. The icteric index was determined in 13 patients and was found to be slightly elevated in one case of subacute hepatitis.

Unfortunately materials were not available for carrying out any of the more elaborate procedures. Others have demonstrated impairment of function in hepatic amebiasis by the levulose tolerance⁹ and the bromsulphalein tests.¹³

TREATMENT

In evaluating the effectiveness of treatment, the following criteria of cure were adopted: (1) complete absence of pain and fever, (2) absence of liver enlargement, (3) absence of subcostal and compression tenderness, (4) normal white blood cell count and sedimentation rate, and (5) absence of *E. histolytica* in the stools.

Treatment consisted of repeated courses of emetine until the criteria of cure were met. The emetine was supplemented with one or more courses of Diodoquin or chiniofon, followed by carbarsone, to eradicate the associated colonic amebiasis presumed to exist in all cases. None of the cases required aspiration or surgical drainage.

Results: Sixty-eight of the 69 patients treated in this manner were cured. One patient with acute hepatitis, who received a total of 22 grains of emetine, failed to meet the criteria of cure. Although he was afebrile and greatly improved clinically, his liver remained enlarged and tender. He was one of our early cases, and in the light of our present knowledge there is good reason to believe that cure could have been effected by further emetine therapy.

Sixty-one of the 69 cases were returned to full military duty. Eight were returned to the United States for further treatment. Of these, five were returned because of unrelated complicating diseases, one had a toxic myocarditis due to emetine, one had unexplained weakness and a thrombophlebitis of the saphenous vein and the last was the only case whose hepatic amebiasis had not been cured.

Six cases (two abscess and four acute hepatitis) had recrudescences of fever and pain in the hospital, which promptly responded to further emetine therapy. These occurred in our early cases before it was realized that continued emetine therapy was indicated until *all* criteria of cure were met.

Three cases of subacute hepatitis had relapses in one to two months. Reinstitution of emetine therapy effected cures in all three.

Obviously, it is difficult to compare these results with those obtained by other methods of treatment, since most reports have dealt principally with abscess and little or no effort has been made to differentiate the acute and chronic forms. In the present series more than half the cases were of the milder forms of the disease in which no mortality was to be expected. The acute forms were seen so early and treated so promptly there was little opportunity for any of the complications to develop. The principal complications of abscess, secondary bacterial infection and rupture or direct extension into the viscera or body cavities have all been shown to increase the mortality.^{1,7}

A number of abscesses, some complicated by bronchohepatic fistula, have been treated with emetine alone without any deaths.^{3, 7, 8, 9} The mortality has been found to vary from 0 to 14.4 per cent with combined emetine and aspiration therapy.^{7, 8} The results following surgical drainage have been the worst, the mortality rates varying between 20 and 40 per cent and even higher, although newer surgical technics have reduced these somewhat.¹ Although the differences in mortality noted between the three types of treatment are to some extent related to the fact that more severe and complicated cases require aspiration or operation, there is sufficient evidence to indicate that operation in itself increases the mortality by converting a sterile into an infected amebic abscess,¹ and there are theoretical grounds for believing that aspiration may also increase the mortality rate.

Although it is recommended that surgical drainage and aspiration be avoided, it should be noted that there are circumstances in which they may be indicated.

Emetine Dosage. Our experience has convinced us that most cases of hepatic amebiasis can be cured with emetine alone, provided the dosage is adequate. The well known cumulative action and toxic effects of emetine, however, are limiting factors that must be taken into account in planning treatment. We now feel that large doses of emetine can be given safely if adequate rest periods are included between courses.

After studying the effects of a variety of treatment schedules in our early cases, we adopted one that combines safety and effectiveness without being too time-consuming. The first course consists of 12 grains given over a 15-day period, one grain daily intramuscularly, with a three-day rest period after the sixth or ninth dose, depending on the patient's reaction to the drug. Most patients tolerate 9 grains well, but occasional patients complain of weakness and exhibit a fall in blood pressure after 6 grains. After a three-day rest period they are able to complete the 12 grain course with no ill effects.

The first course is followed by a two-week rest period, at the end of which emetine therapy is resumed. Courses of six grains each are then alternated with two-week rest periods until the criteria of cure are met. A rest period of two weeks was chosen because it proved to be sufficiently long to prevent the cumulative toxic effects of the drug. Also it was noted that considerable improvement often occurred up to two weeks after the drug was stopped, so that the total dosage of emetine could be kept down to a minimum. Where the rest periods were prolonged beyond two weeks in the face of liver tenderness, leukocytosis or an increased sedimentation rate a clinical recrudescence frequently occurred. In a few of the more acute cases the second and third courses of emetine were given at eight to 10 day intervals with no untoward effects. It may be necessary to shorten the rest periods in this manner if a recrudescence with fever occurs.

The blood pressure and pulse rate were taken twice daily and the patients were kept at complete bed rest during emetine therapy. A few complained

of weakness and exhibited a fall in blood pressure during the first course of 12 grains, but all promptly recovered during their three-day rest period and were able to resume therapy. No toxic effects were seen in the later courses of treatment, with one exception, a thin young nurse, who, through a misunderstanding, received considerably more emetine than outlined. She developed a severe myocarditis demonstrated by electrocardiography and manifested by marked weakness, hypotension and dyspnea.

Nausea and diarrhea were infrequent toxic manifestations and no patients developed neuritis.

Electrocardiograms were taken infrequently as a machine was not always available. Although, for all practical purposes, a close watch on the patient's clinical condition, pulse rate and blood pressure will disclose early myocardial damage, electrocardiograms are desirable at the beginning of each course and on the appearance of unusual cardiovascular symptoms or signs, for maximum safety during prolonged emetine therapy.

The total emetine dose required to effect cure varied with the type of hepatic amebiasis. The abscess cases required the largest doses (average 21.9 grains in 47.6 days), the acute hepatitis somewhat less (average 14.4 grains in 33.4 days), and the subacute and chronic cases the least (average 11.2 and 12.4 grains respectively in 18.1 days) (table 8).

TABLE VIII
Results of Treatment

	Abscess	Acute Hepatitis	Subacute Hepatitis	Chronic Hepatitis
Number of cases treated	7	23	32	7
Number of cases cured	7	22	32	7
Number of relapses	0	0	3	0
Emetine dosage (grains)	21.9 (12-27)	14.4 (6-24)	11.2 (6-26)	12.4 (12-15)
*Effects of treatment on:				
Fever				
Sustained fall	1.9 (1-4)	3.1 (1-12)	4.6 (1-10)	2.0 (2)
Return to normal	9.1 (5-14)	10.2 (1-59)	10.4 (1-25)	6.0 (6)
Pain and tenderness				
Diminished	4.3 (1-8)	3.4 (1-5)	5.3 (1-21)	4.7 (2-8)
Absent	29.6 (4-67)	34.4 (3-119)	17.2 (4-56)	23.6 (12-55)
Leukocytosis				
Return to normal	20.3 (4-27)	21.7 (3-65)	16.5 (10-25)	—
Sedimentation rate				
Return to normal	62.2† (58-66)	28.8 (7-42)	20.7 (7-39)	13.8 (10-17)
Total hospitalization (days)	58.6† (37-72)	66.3 (22-128)	25.8 (15-75)	31.3 (18-66)

* Figures denote days after first dose of emetine. Those within parentheses are the range of variation, the others the average.

† Apparent discrepancy between total hospital days and return of sedimentation rate to normal due to fact that sedimentation rates were determined in only 4 of the 7 cases.

The largest dose of emetine administered to any patient was 27 grains, the smallest 6 grains. One patient with acute hepatitis, and one with subacute hepatitis, were cured with 6 grains. Half of the subacute hepatitis cases were cured with less than 12 grains, usually 8 or 10. Since all three of our relapses occurred in patients who had received less than one full course, we have taken the view that 12 grains is the minimum dose any case of hepatic amebiasis should receive.

Most of the cases of amebic abscess in the literature, cured with emetine alone, received between 10 and 12 grains of emetine, although Berne⁷ reports having used up to 24 grains. The relatively small doses employed suggest that these abscesses were of the early acute type, such as was seen in our series. Payne's recent paper⁸ would seem to indicate that emetine alone is equally effective in the larger more chronic abscesses, since his 24 cases required an average of 36 grains given over a period of 108 days. One of his patients received 60 grains in 120 days.

Response to Emetine (table 8). The response to emetine in our cases was usually so dramatic it was considered diagnostic of the disease.

In two to five days there was usually an appreciable fall in temperature and diminution in liver pain and tenderness. In many patients marked improvement was noted after as little as one grain of emetine. In a few the response was very slow.

The temperature was usually normal by the ninth or tenth day, but liver pain and leukocytosis took considerably longer to clear up completely.

The sedimentation rate took the longest to reach normal, often remaining elevated after the other criteria of cure had been met. This was especially true of the abscess cases in whom the sedimentation rates were elevated for an average of 62.2 days.

Total hospitalization averaged approximately two months in abscess and acute hepatitis and approximately one month in the subacute and chronic hepatitis groups.

Indications for Aspiration. It has been clearly shown that emetine in sufficient dosage is the prime factor in the cure of uncomplicated amebic liver abscess. Aspiration of its contents removes a foreign body factor which may be of importance in some cases.⁷ The advantages to be derived from aspiration are confirmatory evidence of the diagnosis, a shortened convalescence, early detection of secondary bacterial infection, and possibly prevention of rupture or extension into neighboring structures. Against these must be weighed the possible dangers, namely, hemorrhage or rupture into the serosal cavities and the introduction of secondary bacterial infection.

In most cases the prompt response to emetine therapy is sufficient evidence to confirm the diagnosis based on clinical findings. Comparative studies are not available to indicate that convalescence is actually shortened by aspiration, although such an assumption seems reasonable. Nevertheless, the dangers would appear to outweigh the possible advantages of a shortened clinical course.

It has seemed to us, therefore, that the indications for aspiration are: (1) failure of the patient to show any improvement after a full course of 12 grains of emetine, and (2) clinical or roentgen evidence that an abscess located near the surface of the liver is getting larger under emetine therapy.

The technic of aspiration of the liver has been described elsewhere.¹⁷ If the aspirated contents are found to contain bacteria, emetine therapy should be supplemented with one of the sulfonamides or penicillin. A case of chronic amebic abscess with secondary *beta hemolytic streptococcus* infection has recently been successfully treated with aspiration followed by the instillation of penicillin through a fine catheter.¹⁸ The injection of emetine into the abscess cavity¹⁹ does not appear to offer any advantages over the intramuscular route.

Indications for Surgical Drainage. Before the advent of the sulfonamides and penicillin, evidence of secondary bacterial infection was an indication for operation. Bacterial infection is an infrequent complication⁸ so that relatively little experience with these new drugs has been accumulated, but there is reason to believe that many cases will be cured with aspiration and chemotherapy, and they should be tried before operation is attempted.

Aspiration of superficially located abscesses in the left lobe of the liver has been found hazardous and surgical drainage is usually recommended when emetine therapy alone fails.⁸ Fortunately the operative risk is much lower in these than in right lobe abscesses.

Acute rupture of an abscess into one of the serous cavities is usually an indication for surgical drainage, especially when it occurs into the peritoneum or pericardium. Rupture into the pleural space does not necessarily require surgical drainage, unless the abscess contents are secondarily infected. Simple aspiration plus emetine therapy frequently effects a cure.

Ochsner and De Bakey's¹ extraserous approach to the liver would appear to be the method of choice where operation is contemplated. Since operation invariably results in secondary bacterial infection of the abscess, sulfonamides or penicillin should always be administered. Obviously a full course of emetine is also indicated, preferably preoperatively if feasible.

DIAGNOSIS

The early diagnosis of hepatic amebiasis depends chiefly on a careful analysis of the patient's symptoms and physical findings. Roentgen-ray and laboratory examinations often yield helpful collateral evidence but are rarely diagnostic. Confirmation of the diagnosis usually rests on the clear-cut specific response to emetine therapy. More direct confirmation requires the demonstration of amebae in the liver, possibly only in the later stages of the disease when an abscess has developed, and even then amebae are often not found on aspiration. The diagnostic value of a therapeutic trial of emetine in this disease has been amply confirmed.^{8, 20, 21}

The clinical picture of hepatic amebiasis may simulate a great variety of diseases, but they can usually be differentiated without much difficulty.

Most errors in diagnosis are due to a failure to consider the possibility of hepatic amebiasis. This is especially true in the temperate zone where amebiasis is generally regarded as a tropical disease. Numerous studies have indicated that amebiasis is by no means a rare disease in the temperate zone.¹

The conditions to be considered in the differential diagnosis of hepatic amebiasis will depend on the stage of the disease, the predominant symptoms and the presence or absence of complications. In general, they may be grouped as follows: (1) diseases of the right upper quadrant of the abdomen, (2) pulmonary diseases and (3) primary febrile illnesses.

An analysis of the initial diagnoses made on our cases gives some indication of the diagnostic problems involved (table 9). Attention should be

TABLE IX
Diagnoses Made on Admission to the Hospital

	Abscess and Acute Hepatitis (23 Cases)*	Subacute and Chronic Hepatitis (39 Cases)*
Right upper quadrant syndrome	12	39
Hepatitis		
Amebic	5	29
Unclassified	4	6
Cholecystitis	2	1
Gastritis	1	0
Renal calculus	0	1
Pyelitis	0	1
Herpes zoster	0	1
Pulmonary syndrome	7	4
Pleurisy	0	4
Pneumonia	3	0
Upper respiratory infection	4	0
Primary acute febrile illness	7	2
Malaria	3	2
Typhoid	3	0
Dengue	1	0
Diarrheal diseases	6	31
Amebic dysentery	3	30
Acute enteritis	3	1

* Multiple diagnoses account for the discrepancy between the number of cases and the number of diagnoses.

drawn to the fact that the medical officers who saw these patients on admission were keenly aware of the amebiasis problem and were on the lookout for hepatic cases. Multiple diagnoses were common, so that statistical analysis is difficult, but a few important points stand out that are worthy of consideration.

The clinical picture was sufficiently clear to suggest disease in the right upper quadrant of the abdomen in 51 of the 62 cases, and in 44 of these it could be localized in the liver. In 34 the correct diagnosis was made before any laboratory or roentgen-ray examinations were carried out. Liver disease was suspected in almost all of the subacute and chronic hepatitis, but in only one-third of the abscess and acute hepatitis groups.

A diagnosis of pulmonary disease was made in 11 of the 62 cases. It was made in one third of the abscess and acute hepatitis groups and in only four of the 39 subacute and chronic hepatitis cases. Pneumonia or upper respiratory infection was suspected in the former and pleurisy in the latter.

One third of the abscess and acute hepatitis cases were thought to have one of the primary acute febrile illnesses—malaria, typhoid or dengue. Two of the subacute hepatitis groups with fever were diagnosed malaria.

In almost every instance where the diagnosis of hepatic amebiasis was not considered on admission, reëxamination revealed painful enlargement or compression tenderness of the liver or both, indicating the true nature of the disease. The demonstration of *E. histolytica* in the stools added weight to the diagnosis of hepatic amebiasis, but had to be regarded with suspicion since the incidence of amebiasis in all our troops was so high. The absence of *E. histolytica* by no means excluded the diagnosis. Leukocytosis with a relatively low polymorphonuclear count was a helpful point in differentiating hepatic amebiasis from pneumonia and the other acute febrile illnesses. Roentgen-ray examination was particularly useful in excluding pneumonia, but indicated liver disease in only a few instances.

The diagnosis was much simpler, on the whole, in the subacute and chronic hepatic groups. The one disease that might have been confusing, infectious hepatitis, actually presented very little difficulty. The absence of jaundice, anorexia, indigestion, splenomegaly and leukopenia, the infrequent occurrence of nausea and the presence of compression tenderness of the liver favored an amebic etiology and the prompt response to emetine therapy confirmed it. The ineffectiveness of emetine therapy in infectious hepatitis was amply demonstrated in a number of these patients who were found to have *E. histolytica* in their stools. A full course of emetine had no effect on their symptoms or the liver findings, and they ran the usual four to eight week course of this disease.

Of the three cases with involvement of the left lobe of the liver, two were correctly diagnosed on admission and they responded promptly to emetine therapy. The third, an abscess, was thought to have an early pneumonia of the left lower lobe and was treated with sulfathiazole. Chest pain, fever and leukocytosis increased under this form of therapy. Reëxamination of the patient on the fourth day disclosed the fact that the pain was located beneath the left costal margin, radiated to the chest and had all the other characteristics of liver pain. The liver was found to be enlarged and tender with marked compression tenderness and there was a mass beneath the left costal margin. The stools were positive for *E. histolytica*. Rapid recovery followed the institution of emetine therapy.

A secondary diagnosis of amebic dysentery was made on admission in 33 of the 62 cases. Thirty of these fell into the subacute and chronic hepatitis groups, in which, it will be recalled, diarrhea was such a prominent symptom.

A diagnosis of hepatic amebiasis was made fairly promptly in most of the cases. An average of 4.2 days elapsed between admission and the institution of emetine therapy. In 28 cases treatment was started within 24 hours. The longest delay was 20 days.

Chronic amebic abscess, not encountered in this series, presents a number of diagnostic difficulties not mentioned, especially when complicated by extension to neighboring structures. The right upper quadrant syndrome may simulate carcinoma of the liver, stomach or gall-bladder, cirrhosis, amyloid or ecchinococcus disease of the liver, *hepar lobatum*, pyogenic abscess of the liver and abscess complicating peptic ulcer or cholecystitis. The pulmonary syndrome may simulate post-pneumonic empyema, tuberculous pleural effusion, pyogenic lung abscess and bronchogenic carcinoma.^{7, 21}

SUMMARY AND CONCLUSIONS

1. Sixty-nine cases of amebiasis of the liver were encountered in two U. S. Army hospitals in India over a period of 22 months. The clinical features of 62 and the results of treatment in all 69 were discussed.

2. The cases fell into four distinct groups which could be readily differentiated clinically: (1) acute abscess, (2) acute hepatitis, (3) subacute hepatitis and (4) chronic hepatitis. The clinical features and laboratory findings in each were correlated with the known facts about the pathology of the disease. The findings were compared with those seen in chronic amebic abscess, the form of the disease usually described.

3. Emetine therapy alone cured 68 of the 69 cases. One patient was improved but failed to meet the rigid criteria of cure laid down. The necessity for prolonged emetine therapy was stressed and a safe dosage schedule outlined.

4. The clinical classification of hepatic amebiasis makes for a better understanding of the underlying pathology, calls attention to the less commonly recognized forms of the disease and gives some indication of the amount and type of treatment required.

5. The early diagnosis of hepatic amebiasis depends chiefly on a careful analysis of the symptoms and physical findings. Roentgen-ray and laboratory examinations yield helpful collateral evidence, but are rarely diagnostic. Confirmation usually rests on the specific response to emetine therapy. The demonstration of amebae in the liver is possible only in the late stages of the disease.

6. Emetine is the treatment of choice in all forms of hepatic amebiasis. Aspiration and surgical drainage are indicated under special circumstances, especially in late abscess cases.

BIBLIOGRAPHY

1. OCHSNER, A., and DEBAKEY, M.: Amebic hepatitis and hepatic abscess, *Surgery*, 1943, xiii, 460.
2. KLATSKIN, G.: Unpublished data.

3. PAYNE, A. M. M.: Amoebic dysentery in Eastern India, *Trop. Dis. Bull.*, 1945, xlii, 206.
4. PALMER, R. B.: Changes in the liver in amebic dysentery, *Arch. Path.*, 1938, xxv, 327.
5. ROGERS, L.: The rapid cure of amebic dysentery and hepatitis by hypodermic injections of soluble salts of emetine, *Brit. Med. Jr.*, 1912, i, 1424.
6. ROGERS, L.: Amebic liver abscess, *Lancet*, 1922, i, 569.
7. BERNE, C. J.: Diagnosis and treatment of amebic liver abscess, *Surg., Gynec. and Obst.*, 1942, lxxv, 235.
8. ROGERS, L.: Recent advances in tropical medicine, 1929, P. Blakiston's Son and Co., Philadelphia.
9. GREIG, E. D. W.: Amebic abscess of the liver discharged through the lung, *Jr. Trop. Med. and Hyg.*, 1940, xliii, 207.
10. MELENEY, H. E.: The pathology of amebiasis, *Jr. Am. Med. Assoc.*, 1934, ciii, 1213.
11. ROGERS, L.: Amebic liver abscess, *Lancet*, 1922, i, 463.
12. CHEVERS, N. and MACLEAN, Quoted by SCOTT, H. H.: A history of tropical medicine, 1939, The Williams and Wilkins Co., Baltimore.
13. BROWN, P. W. and HODGSON, C. H.: Late results of treatment of amebic abscess and hepatitis of the liver, *Am. Jr. Med. Sci.*, 1938, cxcvi, 305.
14. KILGORE, E. S.: Discussion of Elliott's paper, *Trans. Assoc. Am. Phys.*, 1935, 1, 176.
15. MUNK, J.: X-ray appearances in amebic hepatitis, *Brit. Jr. Radiol.*, 1944, xvii, 48.
16. PANCOAST, H. K.: The roentgenological diagnosis of liver abscess with or without sub-diaphragmatic abscess, *Am. Jr. Roent.*, 1926, xvi, 303.
17. OCHSNER, A., and DEBAKEY, M.: Amebic hepatitis and hepatic abscess, *Surgery*, 1943, xiii, 612.
18. NOTH, P. H., and HIRSHFELD, J. W.: Amebic abscess of the liver with secondary infection. Local treatment with penicillin, *Jr. Am. Med. Assoc.*, 1944, cxxiv, 643.
19. ROYSTER, H. A., HAYWOOD, H. B., and STANFIELD, W. W.: The treatment of amebic abscess of the liver, *Ann. Surg.*, 1936, ciii, 794.
20. ELLIOTT, C. A.: Importance of the therapeutic test for amebiasis in patients presenting symptoms referable to the right lower chest, *Trans. Assoc. Am. Phys.*, 1935, 1, 176.
21. SODEMAN, W. A., and LEWIS, B. O.: Amebic hepatitis, *Am. Jr. Trop. Med.*, 1945, xxv, 35.

SOME COMMON CONDITIONS, NOT DUE TO PRIMARY HEART DISEASE, THAT MAY BE ASSOCIATED WITH CHANGES IN THE ELECTROCARDIOGRAM *

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DURING the past 25 years, the science of electrocardiography has been developed to the point where it has become an important and valuable adjunct to clinical medicine. In more recent years its use in clinical medicine has become widespread. Coincidentally, and perhaps inevitably, with the increased application of electrocardiography, there has developed a tendency towards serious misuse of this valuable and useful method. The major reason for the abuse of the electrocardiogram is that its limitations have not been properly recognized. The frequency with which serious errors in medicine are made because of unjustified conclusions reached from interpretation of electrocardiograms is alarming, and the situation cannot be expected to improve until there is a more general realization of the limitations of electrocardiography. It is my purpose to point out briefly some conditions in which the electrocardiogram may be of value and to indicate in somewhat more detail some of the limitations of the method.

The electrocardiogram is of great value in the detection and classification of the cardiac arrhythmias. Although it is true that in most instances a correct clinical diagnosis of the arrhythmias can be made at the bedside, there are occasional cases in which a correct diagnosis must depend on electrocardiographic findings. This is true when there is auricular flutter with constant auriculoventricular block and a regular ventricular rhythm at a relatively slow rate, and when no clue can be obtained from physical examination because the patient is too ill to be exercised. When there is a totally irregular rhythm due to many auricular or ventricular premature beats, it may be impossible clinically to differentiate with certainty such an arrhythmia from auricular fibrillation. A diagnosis of ventricular tachycardia, although often suspected clinically, always requires electrocardiographic confirmation. Finally, even when one can be quite sure of the clinical diagnosis of an arrhythmia, electrocardiographic confirmation is desirable and comforting.

The electrocardiogram may be of real value in the recognition of myocardial infarction. In most instances of acute myocardial infarction, the electrocardiographic tracing will not only reveal the presence of the infarction but may allow one to localize it with a reasonable degree of certainty to the anterior, posterior or lateral wall of the ventricle. The electrocardiogram will be of value, not only in the recognition of myocardial infarction,

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but also in following the course of the disease. Serial tracings taken during the course of an acute myocardial infarction may be useful in following the progress of the disease and may give helpful information in regard to the healing of the infarction. Furthermore, it may be possible to identify old and previously unrecognized cases of myocardial infarction through the persistence of certain residual changes in the electrocardiogram. In this respect, however, its value is not great, since certain extracardiac influences may produce changes of a similar nature.

The electrocardiogram may be of value during the course of certain systemic diseases, such as rheumatic fever, trichinosis or diphtheria, to indicate when the heart has become involved. Electrocardiographic evidence in such instances may be the only evidence obtainable to indicate if and when cardiac involvement has occurred.

Less frequently the electrocardiogram may be of value in revealing or making one suspicious that a patient has been taking certain drugs, notably digitalis. At times, when one cannot be certain from the history that a patient has been taking digitalis, an electrocardiogram may reveal the typical findings of digitalis effect. The presence of a normal electrocardiogram, however, in such a case is not positive proof that the patient has not been taking digitalis. The diagnosis of digitalis intoxication, as a rule, depends on clinical findings and is not information that can be gleaned from the electrocardiogram. Although the changes in the electrocardiogram due to the effect of digitalis may at times be helpful, in many instances these changes are misinterpreted as being evidence of myocardial disease. When it is important to determine whether or not the changes in a given electrocardiogram are due to myocardial disease or to the effect of digitalis, the drug should be withdrawn, and if the changes in question are due to its effect, they should disappear within a period of three weeks. Changes due to digitalis will usually disappear more promptly, but it should be remembered that they may sometimes persist for as long as three weeks after the drug has been discontinued.

The electrocardiogram, then, may be of great value in the detection and classification of the cardiac arrhythmias and in the recognition of acute myocardial infarction. It may also be of value in determining when the heart has become involved in the course of certain systemic diseases and in revealing the influence of certain drugs, principally digitalis.

With this brief discussion of the value of electrocardiography as an introduction, we may discuss in somewhat more detail some of the limitations of the method. It should be stressed from the outset that as compared to other methods of examination the electrocardiogram provides very little information as to function of the heart or as to prognosis. The electrocardiogram is often entirely normal in individuals suffering from severe heart disease and advanced congestive heart failure. Many patients with angina pectoris on slightest exertion and severe coronary sclerosis will exhibit a normal electrocardiogram while at rest. In those patients with severe coro-

nary artery disease and normal resting electrocardiograms, exercise will effect transient changes in the tracing which reveal the coronary disease in a fairly large number of cases. There remains, however, an appreciable number of patients with severe coronary artery disease and angina pectoris who have normal electrocardiograms, even immediately after exercise. Such patients have obvious functional impairment, yet exhibit no abnormal changes in the electrocardiogram. 'On the other hand, there may be striking changes in the electrocardiogram in the absence of heart disease and when there is no functional impairment of the heart. It is clear, then, that as far as function is concerned, the electrocardiogram is not a reliable measuring rod and if depended upon, may be dangerously misleading.' It is equally incorrect to look to the electrocardiogram for information regarding prognosis in a patient with heart disease. In many individuals with serious heart disease who have had one or more myocardial infarctions in the past the changes in the electrocardiogram will have completely disappeared after the infarctions have healed. Such individuals may have marked coronary artery sclerosis, yet no clue as to the serious nature of the heart disease may be gained from a study of the single electrocardiographic tracing. On the other hand, there may be striking changes in the electrocardiogram in certain individuals who have no evidence of heart disease and who may be expected to live for many years. The Wolff-Parkinson-White syndrome, where there are the changes of bundle branch block with a short PR interval, is an example of such a condition. A serious error in prognosis would be made by one who interpreted these changes as indicating poor prognosis or impairment of function, for in such individuals the heart is normal, the bizarre findings in the electrocardiogram being due to short circuiting of the conduction impulse through the bundle of Kent.

A third cause for error in the interpretation of the electrocardiogram lies in an adherence to too rigid criteria for normality in the electrocardiographic tracing. Recent reports of Stewart and Manning³¹ and Graybiel, McFarland, Gates and Webster,¹³ who studied electrocardiograms made on large numbers of healthy young adults in the Armed Forces, show clearly that our present standards of normality in the electrocardiogram are in need of revision. For example, the term "sinus bradycardia" is usually used to denote rates below 60. Graybiel and his coworkers found that one-third of their cases had rates between 50 and 60. They believe the term "sinus bradycardia" should be reserved for rates below 45. Notching of the P-wave, usually considered abnormal, occurred in 27 per cent of their cases of normal healthy males. The upper limit of normality in the PR interval is usually considered to be between .18 and .20 second, depending on the age of the individual. In the series of Graybiel et al. the PR interval was .19 second in 19 cases, .20 second in 33 cases, .21 second in four cases, .22 second in eight cases and .24, .25, .26 and .28 second in one case each. Four cases in the Stewart and Manning series presented a PR interval of over .24 second, the longest one of which was .36 second. According to present

standards .10 second is the upper limit of normal for the QRS interval. In the combined series of 1500 cases there was a QRS interval of over .10 second in 47 cases. In one case of Grabiel et al. the QRS interval was .13 second. They concluded that a QRS interval as long as .13 second may be observed in young persons without evidence of heart disease and that a QRS interval of .11 second is found with sufficient frequency in young, healthy adults to suggest that it is not necessarily of pathological significance. Notching and slurring of the QRS complex, often considered of pathological significance, occurred in the total of 1500 cases 36 times in Lead I, 39 times in Lead II and in 210 cases in Lead III. An amplitude of the QRS complex no greater than 5 mm. in the standard limb leads occurred in 16 cases. Left and right axis deviation occurred with sufficient frequency to show that deviation of the electrical axis in itself is not necessarily of pathological significance. There were 95 instances of left axis deviation and 64 instances of right axis deviation occurring among the 1500 normal, healthy adults.

Displacement of the ST segment of more than 1 mm. was a rare occurrence in this series of normal healthy adults. The ST segment was displaced upward more than 1 mm. in Lead I in 6 instances, in Lead II in 35 instances, and in Lead III in 7 instances. Downward displacement of more than 1 mm. occurred once in Lead I, not at all in Lead II, and three times in Lead III.

In the entire series of 1500 cases there was no instance of an inverted or diphasic T_1 . In two instances T_2 was inverted, and in two instances it was diphasic. T_1 , on the other hand, was inverted or diphasic in one-fifth of all the cases of Graybiel, et al. and in 28 per cent of Stewart and Manning's cases.

These results show that "the range of variation in the electrocardiogram of normal young airmen is considerably greater than the present standards would lead one to expect, and a relatively large number of records show characteristics which hitherto have been considered diagnostic of heart disease". The obvious conclusion is that the normal in electrocardiography extends well into what has been commonly regarded as the abnormal range. These results emphasize the great individual variation in electrocardiographic pattern and the wide range of normal values, so that we are coming to realize that many changes in the electrocardiogram that have previously been considered definitely abnormal, in a great many instances actually are not. Until the present criteria for normality are revised these minor changes that may occur in normal individuals should be disregarded when there is lack of clinical correlation. For that matter, any electrocardiographic changes should be viewed with skepticism when the findings cannot be correlated clinically with the patient.

Most of the serious errors of interpretation of the electrocardiogram may be found in the interpretation of the changes that occur in the ventricular complex, including the ST segment and T-wave. There is fairly widespread belief that the changes in this particular part of the electrocardio-

gram specifically indicate myocardial disease or disease of the coronary arteries. This misconception has undoubtedly led to the more serious errors of electrocardiographic interpretation and is in large part due to a failure of recognition of the non-specificity of changes in this portion of the tracing. In order to emphasize the lack of specificity of these changes, I wish to present a list of some of the more common conditions, not due to primary disease of the heart, which may bring about changes in the electrocardiogram similar to those commonly attributed to coronary sclerosis and diffuse myocardial disease.

1. *Drugs*: Many drugs produce changes in the electrocardiogram. The effect of digitalis is well known, as is that of quinidine. Less well recognized is the effect of other drugs. The anti-malarial drugs, plasmochin, atabrine and quinine, cause electrocardiographic changes.¹⁰ Plasmochin increases the amplitude of the QRS complex and T-wave. In some cases it causes elevation of the ST segment which may stimulate, in some degree, those changes which occur after a coronary thrombosis. Atabrine, on the other hand, decreases the amplitude of the QRS and the T-waves and restores the ST segment to the iso-electric level after it has been elevated by plasmochin. Quinine has a similar effect to atabrine, but to a lesser degree. Adrenalin, ergotamine tartrate, atropine, emetine and mechoyl^{16, 18} are other drugs that may affect the ST segment and the T-wave in the electrocardiogram. Inhalation of tobacco smoke brings about an increase in the rate of the heart and not infrequently causes lowering or inversion of the T-waves.¹⁴ These changes are transient and disappear promptly when the subject stops smoking. They are due to the effect of the nicotine in the tobacco smoke.

It is important, then, that electrocardiograms be interpreted with a knowledge of the drugs the patient has been taking so that changes caused by such drugs may not be mistakenly attributed to disease of the heart. The changes in the electrocardiogram due to drugs disappear after the drugs are withdrawn.

2 *Exercise*: Excessive exercise in normal individuals will produce depression of the ST segments and flattening or inversion of the T-waves (figure 1).^{18, 20} These changes are most likely related to the reduction in coronary blood flow incident to the tachycardia that occurs with excessive exercise and are quite transient and disappear promptly with the decline in rate of the heart. For the same reason similar changes may occur in the electrocardiogram in patients who have paroxysmal auricular tachycardia or paroxysmal auricular fibrillation. These changes may be noted after the subsidence of the attack, and unless the attack is of extremely long duration, they are transient and disappear within a few hours or days after the tachycardia is terminated.

3. *Acute Infection*: Inversion of the T-wave and changes in the ST segment have been described as occurring during the course of various acute infections: pneumonia, trichinosis, diphtheria, typhoid fever, typhus fever, influenza, periarteritis nodosa, undulant fever, and pulmonary tuberculosis.²⁸

These changes are transient and disappear with the subsidence of the acute infectious process.

4. *Pericarditis*: Fairly characteristic electrocardiographic changes may appear in acute and in chronic pericarditis. It is permissible to consider

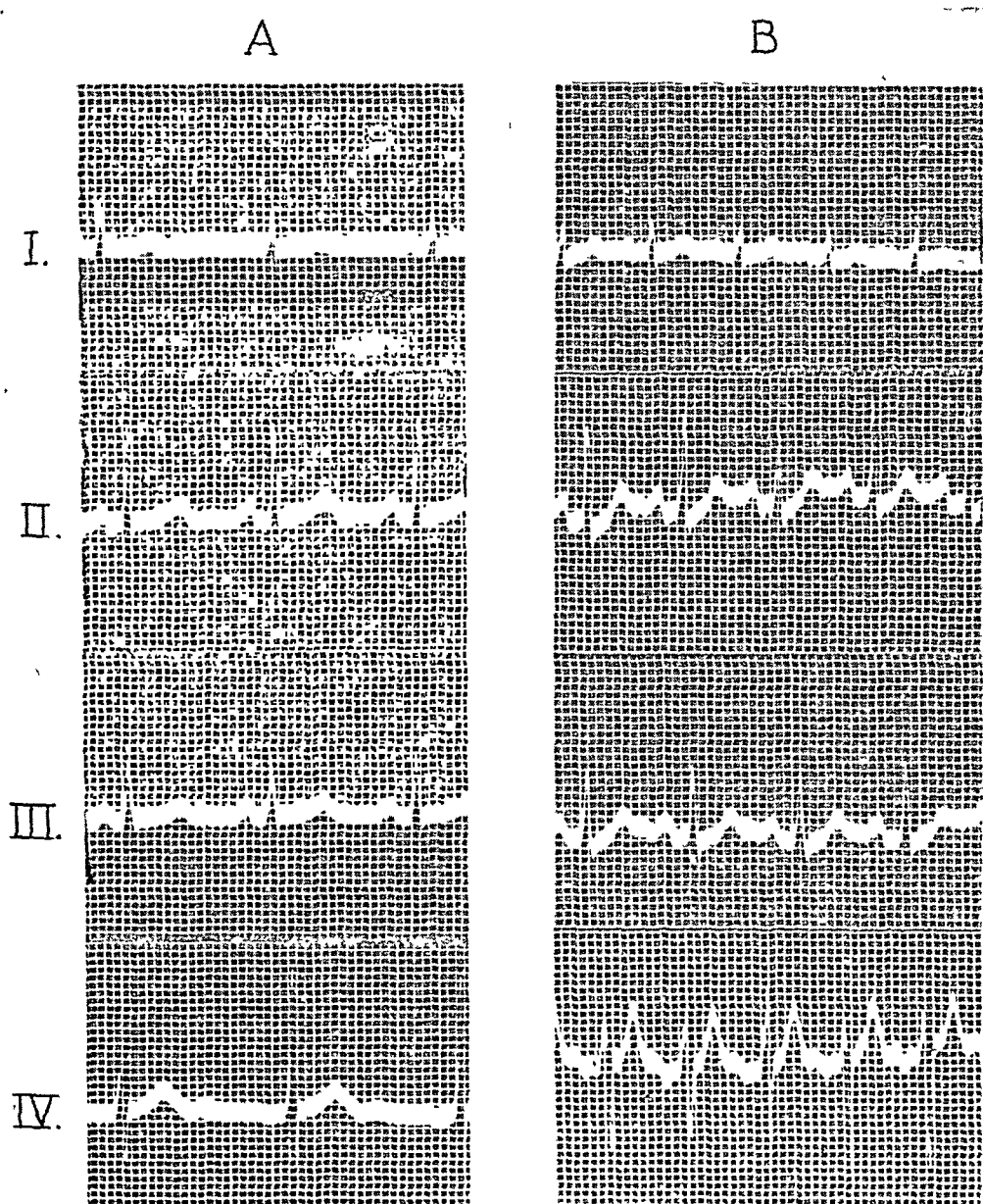


FIG. 1. A. Electrocardiogram made on a normal, healthy medical student at rest. B. Record made immediately after exercise.

pericarditis as an extra-cardiac lesion, and it is considered so here because the electrocardiographic changes, either in chronic or acute pericarditis, may be similar to those caused by diffuse myocardial disease resulting from coronary arteriosclerosis. In both acute and chronic pericarditis, the clinical picture

is usually so clearcut as to preclude the necessity for electrocardiographic evidence in differentiating the two conditions.

5. *Metabolic Disorders*: In simple obesity there may be changes in the electrocardiogram, usually characterized by low amplitude of the QRS complex and of the T-wave. These changes are similar in many respects to those that may be seen in hypothyroidism. In the latter condition, however, changes in the T-waves are usually more marked, and there may be inversion of these waves in all leads occasionally with depression of the ST segments. Following thyroid medication the amplitude of the QRS complexes is increased, and the record is restored to normal. Changes of a different nature have been described in hyperthyroidism,⁸ with again the major changes occurring in the terminal portion of the QRS complex. The T-waves in hyperthyroidism are often increased in amplitude.

✓ Clagett has described minor changes in the electrocardiogram during the course of artificial fever therapy.⁴ The changes are mainly variations in amplitude of the various components of the electrocardiogram, but in a few instances there may be slight ST segment depression. These changes are transient, and are considered insignificant by the author, who believes they are due to the tachycardia that accompanies the hyperpyrexia. ✓

Alterations in the acid-base balance in the body may lead to changes in the electrocardiogram that may simulate those due to coronary sclerosis and diffuse myocardial disease. Alkalosis,^{2, 20, 31} produced either by overventilation or by the ingestion of sodium bicarbonate, is accompanied by a reduction in the amplitude of the T-waves. Acidosis, on the other hand, produced experimentally by the ingestion of ammonium chloride, causes an increased amplitude of the T-waves. Changes that may occur in the electrocardiogram during the course of the hyperventilation syndrome, for example, are occasionally marked and may be confused with those that occur after myocardial infarction.³¹ It is believed that these changes are due to changes in the pH of the blood, since alkalosis brought about by other means may cause similar changes in the electrocardiogram. The fact that electrocardiographic changes similar to those occurring in myocardial infarction may occur in patients with anxiety neurosis and the hyperventilation syndrome is important, since most of them have chest pain which, without careful evaluation, may be mistaken for angina pectoris. It is very important, therefore, to recognize that the hyperventilation syndrome alone may lead to changes in the T-waves and the ST segment that simulate those found in myocardial disease and myocardial infarction.

Case 1. A young married woman entered the hospital complaining of severe shortness of breath and "heart trouble" of a few weeks' duration. She was greatly disturbed emotionally and hyperventilated almost continuously while awake. Except for moderate obesity the physical examination was normal. The heart was not enlarged, and there were no murmurs. The blood pressure was normal. Roentgen-ray and fluoroscopy of the heart revealed no abnormalities in the size or shape of the cardiac silhouette. The electrocardiogram (figure 2) was distinctly abnormal, the most marked change being in Lead II, where the T-wave was sharply inverted.

Bellet and Dyer³ observed electrocardiographic changes in all of their cases of diabetic acidosis. The chief alterations observed were prolongation of the QT interval, lowering or inversion of T-waves and depression of ST segments. These changes were transient and were most marked, not during coma, but about 24 hours later when the patients were clinically improved.

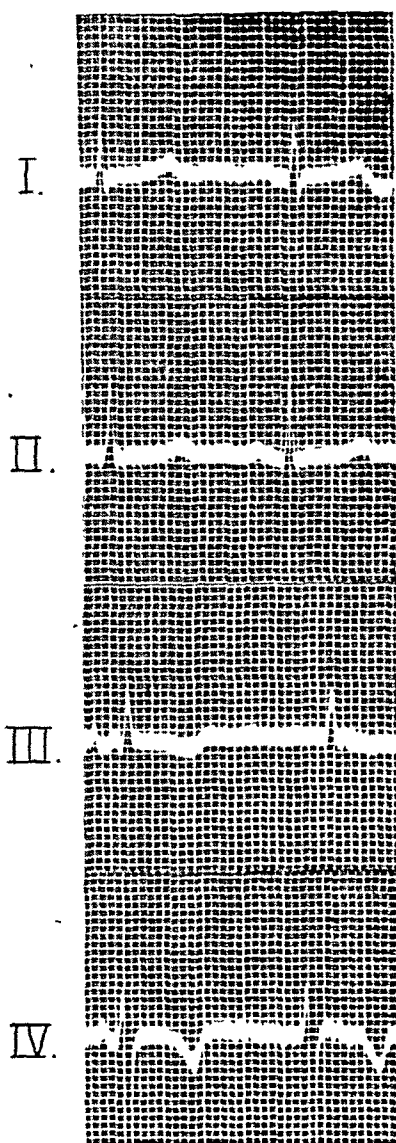


FIG. 2. Abnormal electrocardiogram with T_i inversion in a patient with a marked anxiety state and hyperventilation syndrome.

One patient whose acidosis was non-diabetic in origin exhibited similar changes in the electrocardiogram.

The administration of insulin in amounts sufficient to cause hypoglycemia will produce changes similar to those found in diabetic acidosis. These changes not only occur in patients who have diabetes, but have been noted in

non-diabetic patients who have been subjected to insulin shock therapy. In a few persons with spontaneous hypoglycemia or hyperinsulinism similar changes have occurred.

Case 2. A 39 year old male had had numerous attacks of constrictive precordial pain associated with numbness in the left arm. The pain varied from mild to severe, and lasted from one to two hours. There was no relationship to exertion, and no attack had occurred within two hours after a meal. The physical examination was negative. No pain or electrocardiographic changes could be induced by exertion. However, a typical attack of pain and marked electrocardiographic changes (figure 3) could be induced by insulin. The attacks were prevented by a low carbohydrate, high protein diet.

Harrison and Finks¹⁷ report the case of a 27 year old female who had typical attacks of angina pectoris, and whose attacks were not related to exertion, but could be induced by insulin and relieved by either nitroglycerin or orange juice. During the attacks elevation of the ST segments in the electrocardiogram was noted.

Fox and Messeloff⁸ have described transient electrocardiographic changes occurring during the course of serum sickness. In their case, the QRS complex was diminished in amplitude, as was the T-wave in Leads II, III and IV. There were only minor ST segment changes. In 10 days the electrocardiogram had become normal.

Electrocardiographic changes are not uncommon in certain vitamin deficiency diseases.^{26, 27} In beriberi and in minor grades of vitamin B₁ deficiency, T-wave abnormalities, as well as low amplitude of the QRS complexes, have been described. The electrocardiographic changes in pellagra are mainly characterized by lowering and inversion of the T-waves. The administration of thiamin chloride or nicotinic acid results in a prompt return of the electrocardiogram to normal. Rachmilewitz and Braun²⁷ proposed that the changes in the electrocardiogram that may occur during the course of pellagra are metabolic in origin as a result of a coenzyme deficiency in the heart muscle. This impression was confirmed by Govier¹² who found that coenzyme 1 is reduced by 70 per cent to 83 per cent of normal in cardiac muscle rendered ischemic by coronary artery ligation. Nicotinamide given intravenously before coronary ligation protected to a great extent against the breakdown of coenzyme 1.

Electrocardiographic changes are frequently observed in the anemias of both the acute and chronic types. In the chronic anemias, such as untreated pernicious anemia or sickle cell anemia, the changes may be due to actual changes in the myocardium since many such patients also have cardiac enlargement. Usually, unless the anemia is of very long duration, the electrocardiographic changes will disappear when the anemia is corrected. Scherf and Klotz²⁸ have described electrocardiographic changes occurring in the acute anemia due to sudden blood loss. These changes were characterized by lowering to inversion of the T-waves and depression of the ST segments. Slightly lowered amplitude of the QRS complex was occasionally observed.

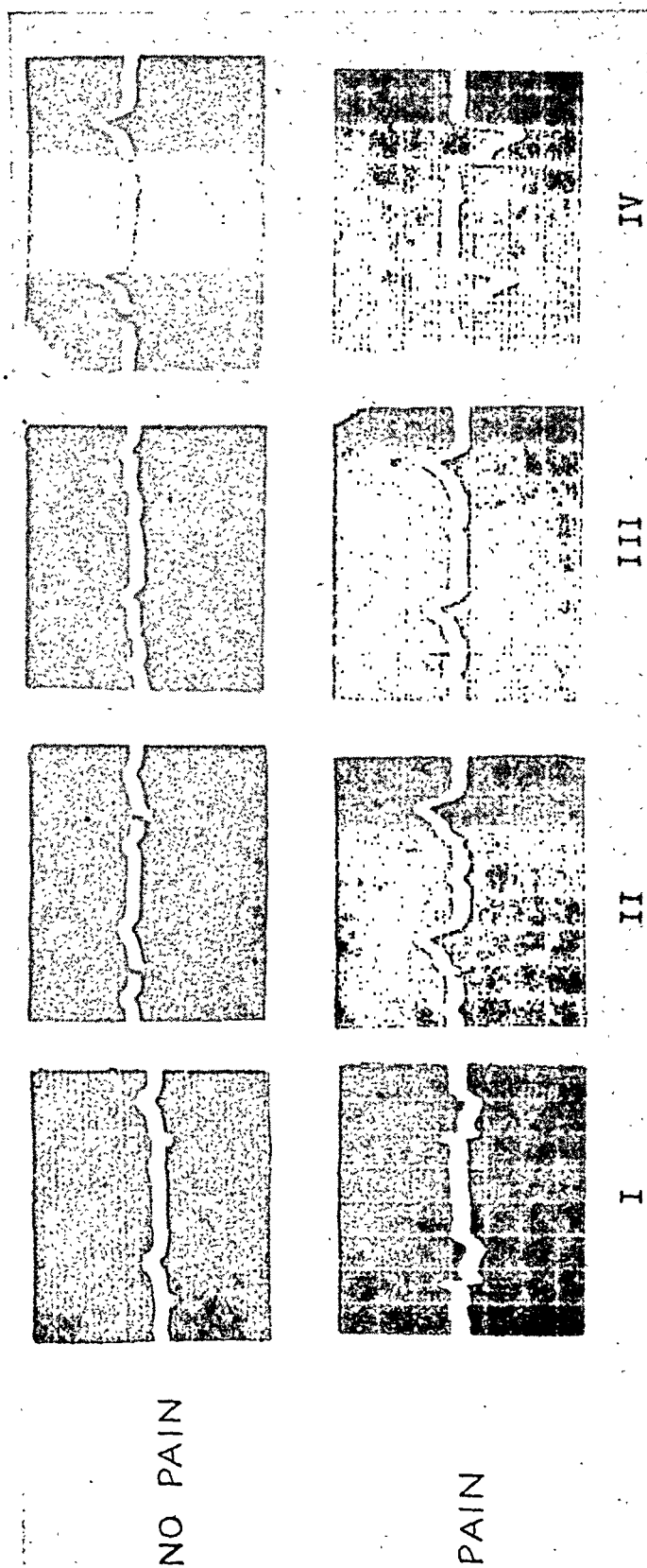


FIG. 3. These electrocardiograms show the marked ST segment displacement that may be induced by insulin. See text, case 3.

The changes developed in the absence of shock, without severe anemia and were independent of the hemoglobin level. They disappeared in two to nine days.

Carbon monoxide poisoning may be associated with changes in the electrocardiogram.³⁰ The commonest changes are lowering or inversion of the T-waves, with or without slight displacement of the ST segments. Intra-ventricular block has been reported, but this occurs more rarely.

6. *Renal Disease*: Variations in the serum potassium level may lead to changes in the electrocardiogram.^{4, 20} In patients with uremia and potassium retention, intraventricular conduction defects have been described, along with increased amplitude of the T-waves in all leads. With potassium depletion, decreased amplitude of the T-waves and slight ST segment depression may occur. These changes disappear after the potassium deficit in the serum is corrected. Electrocardiographic changes occur in acute glomerulonephritis in a high percentage of cases.¹ The most striking changes are seen in the T-waves, with low amplitude to inversion, and there may also be depression of the ST segments. In some cases the changes may be strikingly similar to those due to acute myocardial infarction.

Case 3. A 14 year old girl entered the hospital with the characteristic findings of acute glomerulonephritis. She was critically ill at the time of admission, and remained so for a period of two weeks when clinical improvement began. An interesting series of electrocardiograms was obtained (figure 4), revealing changes very similar to those that occur in myocardial infarction. As the patient improved clinically, the electrocardiogram changed so that by the time the patient was discharged from the hospital it had become almost normal.

7. *Acute Upper Abdominal Conditions*: Acute inflammatory lesions in the upper abdomen may be associated with electrocardiographic changes that may be similar in many respects to those caused by disease of the coronary arteries. Such electrocardiographic changes have been described in acute pancreatitis,^{10, 11, 15} in uncomplicated disease of the gall-bladder,^{6, 7, 24} bleeding peptic ulcer,²⁸ ruptured peptic ulcer.²⁵ These changes are transient and disappear after the removal of the acute abdominal focus. It is important that this fact be recognized, since there is occasionally difficulty in determining whether severe upper abdominal pain is arising from below or above the diaphragm. Unless one is aware of the fact that electrocardiographic changes may occur in certain acute upper abdominal lesions, he may be misled on the basis of electrocardiographic findings into attributing the origin of the pain to the heart rather than to the abdomen.

8. *Pulmonary Embolism*: Embolus to a large branch of the pulmonary artery may be associated with changes in the electrocardiogram which may resemble those due to coronary sclerosis. Slight depression of the ST segments and inversion of the T-waves, especially of T₂ and T₃, may occur. A deep S-wave in Lead I and Q-wave in Lead III also often appear.

9. *Autonomic Nervous System Imbalance*: Certain patients with neuro-circulatory asthenia may show T-wave inversion in Leads II and III.^{22, 33}

These findings tend to vary from time to time so that occasionally the T-waves may be upright, having previously been inverted. Increased amplitude of the T-wave may also occur in this disease.

There is evidence to indicate that fear may cause changes in the electrocardiogram in persons with normal hearts (figure 5). Mainzer and Krause²³ made electrocardiograms on patients on the operating table immediately before the induction of a general anesthetic. Abnormal electrocardiographic records, as compared with a tracing made on the previous day, were obtained

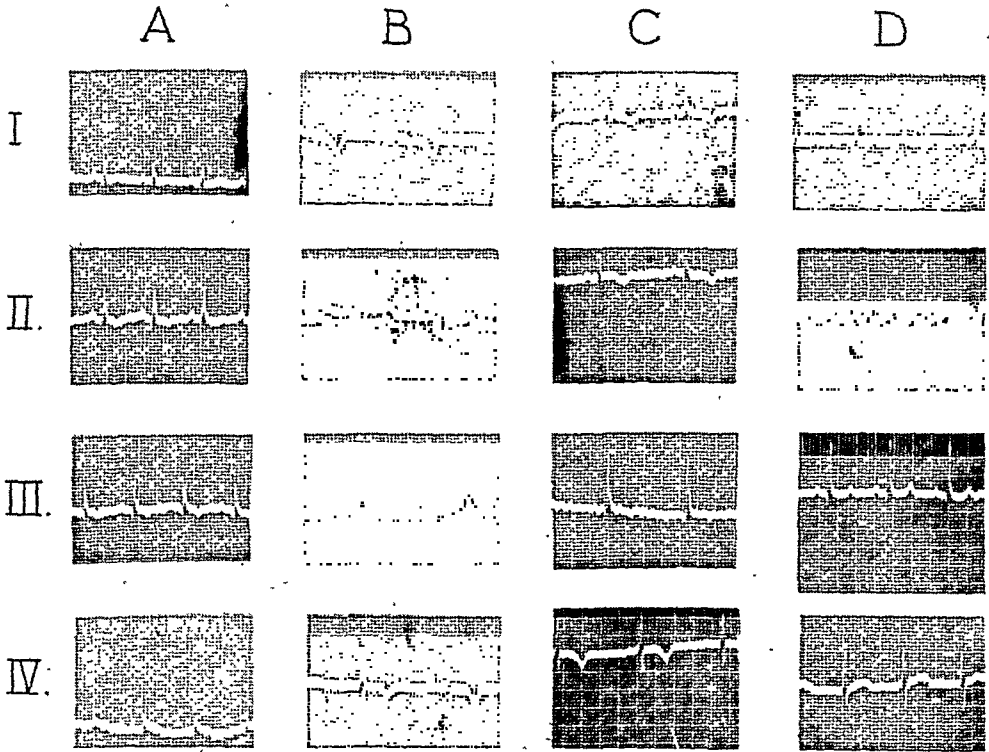


FIG. 4. A. Sept. 22, 1943, shortly after admission to the hospital.
 B. Oct. 4, 1943, the patient still critically ill, blood pressure elevated, marked nitrogen retention.
 C. Oct. 8, 1943, at this time clinical improvement has begun.
 D. Oct. 25, 1943, almost complete clinical recovery. The electrocardiogram also is now almost normal.

in two-fifths of their 53 cases. The changes noted consisted in depression of the ST segment, flattening or inversion of the T-waves, these changes being similar to those appearing in coronary insufficiency. In other cases, increased amplitude of the P-waves and the T-waves with sharply pointed P- and T-waves was noted. These changes are similar to those that may be seen in neurocirculatory asthenia.

The foregoing would seem to indicate, then, that the changes in the terminal portion of the QRST complex, so often considered specific of myocardial disease, are far from being so, since we are able to present a list, ad-

A

B

I.

II.

III.

IV.

FIG. 5. A. This record was made on an 11-year old girl who was admitted to the hospital for a corrective eye operation. This electrocardiogram was made two days before operation.

B. Record made on the same patient on the operating table, immediately pre-operatively. No pre-operative medication had been given. The child was very apprehensive. Note that T_2 has become almost isoelectric, and T_3 has become definitely inverted. Another record made three days after operation was normal.

mittedly incomplete, of 47 conditions, none of which is due to primary heart disease, but all of which may produce changes in the electrocardiogram similar to those caused by coronary sclerosis and myocardial disease. An appreciation of this fact will make for more rational interpretation of the electrocardiogram and will avoid some of the errors of interpretation that now occur.

CONCLUSIONS

1. The electrocardiogram is of great value in the recognition of the cardiac arrhythmias and in the detection of myocardial infarction. It may be useful in determining if and when the heart has become involved during the course of certain systemic diseases, and less frequently, in determining whether or not an individual has been taking certain drugs, notably digitalis.

2. A more widespread recognition of the limitations of electrocardiography is desirable.

3. Little information regarding function of the heart or prognosis can be obtained from the electrocardiogram.

4. The present accepted standards of normality for the electrocardiogram are incorrect, since too many normal healthy young adults show changes which, according to present standards, are diagnostic of heart disease.

TABLE I

Some Conditions, Not Due to Primary Disease of the Heart, That May Be Associated with Changes in the Electrocardiogram Similar to Those Caused by Coronary Sclerosis and Myocardial Disease

- | | |
|--|--|
| <p>1. <i>Drugs</i></p> <ul style="list-style-type: none"> a. digitalis b. quinidine c. quinine d. atabrine e. plasmochin f. adrenalin g. ergotamine tartrate h. atropine i. mecholyl j. emetine k. tobacco smoke (nicotine) <p>2. <i>Exercise</i></p> <p>3. <i>Acute Infections</i></p> <ul style="list-style-type: none"> a. pneumonia b. trichinosis c. diphtheria d. typhoid fever e. typhus fever f. influenza g. periarteritis nodosa h. undulant fever i. pulmonary tuberculosis <p>4. <i>Pericarditis</i></p> <ul style="list-style-type: none"> a. acute b. chronic <p>5. <i>Metabolic Disorders</i></p> <ul style="list-style-type: none"> a. obesity b. hypothyroidism | <p>5. <i>Metabolic Disorders</i> Cont'd</p> <ul style="list-style-type: none"> c. hyperthyroidism d. artificial fever e. acidosis f. alkalosis g. hypoglycemia h. hyperventilation syndrome i. serum sickness j. thiamin chloride deficiency k. nicotinic acid deficiency l. acute blood loss m. chronic anemias n. carbon monoxide poisoning <p>6. <i>Renal Disease</i></p> <ul style="list-style-type: none"> a. serum potassium retention b. serum potassium depletion c. acute glomerular nephritis <p>7. <i>Acute Upper Abdominal Disease</i></p> <ul style="list-style-type: none"> a. acute pancreatitis b. uncomplicated gall-bladder disease c. bleeding peptic ulcer d. perforated peptic ulcer <p>8. <i>Pulmonary Embolism</i></p> <p>9. <i>Autonomic Nervous System Imbalance</i></p> <ul style="list-style-type: none"> a. neurocirculatory asthenia b. fear |
|--|--|

5. The major cause for the more serious mistakes in interpretation is the widespread belief that changes in the Q_RST complex and especially the ST segments and T-waves are specific for myocardial disease. A list of 47 conditions, not due to primary heart disease, in which similar changes may occur, is presented in proof of the nonspecificity of these changes.

BIBLIOGRAPHY

1. ASH, R., RUBEN, J. I., and RAPPOPORT, M.: Electrocardiographic variations in acute glomerulonephritis, *Am. Jr. Dis. Child.*, 1944, lxvii, 106-116.
2. BASHIER, P. S., SHRADER, E. L., and RONZONI, E.: The effects of alkalosis and of acidosis upon the human electrocardiogram, *Am. Heart Jr.*, 1939, xvii, 169-186.
3. BELLET, S., and DYER, W. W.: The electrocardiogram during and after emergence from diabetic coma, *Am. Heart Jr.*, 1937, xiii, 72-87.
4. BROWN, M. R., CURRENS, J. H., and MARCHAND, J. F.: Muscular paralysis and electrocardiographic abnormalities, *Jr. Am. Med. Assoc.*, 1944, cxxiv, 545-549.
5. CLAGGETT, A. H., JR.: The electrocardiographic changes following artificial hyperpyrexia, *Am. Jr. Med. Sci.*, 1944, ccviii, 81-95.
6. CLARK, N. E.: Electrocardiographic changes in active duodenal and gall-bladder disease, *Am. Heart Jr.*, 1945, xxix, 628-632.
7. FITZHUGH, T., and WOLFERTH, C. C.: Cardiac improvement following gall-bladder surgery, *Ann. Surg.*, 1935, ci, 478-483.
8. FOX, T. T., and MESSELOFF, C. R.: Electrocardiographic changes in a case of serum sickness due to tetanus antitoxin, *New York State Jr. Med.*, 1942, xlii, 152-154.
9. GORDON, G., SOLEY, M. H., and CHAMBERLAIN, F. L.: Electrocardiographic features associated with hyperthyroidism, *Arch. Int. Med.*, 1944, lxxiii, 148-153.
10. GOTTESMAN, J., CASTEN, D., and BELLER, A. J.: Electrocardiographic changes associated with acute pancreatitis, *Proc. Soc. Exper. Biol. and Med.*, 1942, xlix, 365-367.
11. GOTTESMAN, J., CASTEN, D., and BELLER, A. J.: Changes in the electrocardiogram induced by acute pancreatitis, *Jr. Am. Med. Assoc.*, 1943, cxxiii, 892-894.
12. GOVIER, W. M.: The effect of experimental coronary artery ligation on the coenzyme 1 and cocarboxylase content of the myocardium of the dog, *Am. Heart Jr.*, 1945, xxix, 384-389.
13. GRAYBIEL, A., MCFARLAND, R. A., GATES, D. C., and WEBSTER, F. A.: An analysis of the electrocardiograms obtained from 1000 young healthy aviators, *Am. Heart Jr.*, 1944, xxvii, 524-549.
14. GRAYBIEL, A., STARR, R. S., and WHITE, D. D.: Electrocardiographic changes following the inhalation of tobacco smoke, *Am. Heart Jr.*, 1938, xv, 89-99.
15. GRUBNER, R. S.: Electrocardiographic changes in abdominal disease, *Jr. Am. Med. Assoc.*, 1944, cxxiv, 122-123.
16. HARDGROVE, M., and SMITH, E. R.: Effects of emetine on the electrocardiogram, *Am. Heart Jr.*, 1944, xxviii, 752-757.
17. HARRISON, T. R., and FINKS, R. M.: Glucose deficiency as a factor in the production of symptoms referable to the cardiovascular system, *Am. Heart Jr.*, 1943, xxvi, 147-163.
18. HARTWELL, A. S., BURRETT, J. B., GRAYBIEL, A., and WHITE, P. D.: The effect of exercise and of four commonly used drugs on the normal human electrocardiogram with particular reference to T-wave changes, *Jr. Clin. Invest.*, 1942, xxi, 209-417.
19. HERMANN, H. L., and SHAPIRO, B. G.: Effects of plasmoquin, atabrine and quinine on the electrocardiogram, *Brit. Heart Jr.*, 1943, v, 131-133.
20. KEITH, N. M., BURCHELL, H. B., and BAGGENSTOSS, A. H.: Electrocardiographic changes in uremia associated with a high concentration of serum potassium: Report of 3 cases, *Am. Heart Jr.*, 1944, xxvii, 817-844.

21. LAURENCE, J. S., and ALLOTT, E. N.: Heart changes in alkalosis, *Brit. Heart Jr.*, 1943, v, 128-130.
22. LOGUE, R. B., HANSON, J. F., and KNIGHT, W. A.: Electrocardiographic studies in neurocirculatory asthenia, *Am. Heart Jr.*, 1944, xxviii, 574-577.
23. MAINZER, F., and KRAUSE, M.: The influence of fear on the electrocardiogram, *Brit. Heart Jr.*, 1940, ii, 221-230.
24. MOSCHCOWITZ, E.: The electrocardiogram in uncomplicated disease of the gall bladder and the change induced by operation, *Jr. Mt. Sinai Hosp.*, 1944, x, 633-635.
25. MURPHY, F. D., and LIVEZEY, M. M.: Electrocardiographic changes simulating those of acute myocardial infarction in a case of perforated gastric ulcer, *Am. Heart Jr.*, 1944, xxviii, 533-537.
26. PARDEE, H. E. B.: Clinical aspects of the electrocardiogram, 1941, Paul B. Hoeber, Inc., New York.
27. RACHMILEWITZ, M., and BRAUN, K.: The presence of electrocardiographic changes in nicotinic acid deficiency and their elimination by nicotinic acid, *Am. Heart Jr.*, 1944, xxvii, 203-208.
28. SCHERF, D., and KLOTZ, S. D.: Electrocardiographic changes after acute blood loss, *Ann. Int. Med.*, 1944, xx, 438-452.
29. SENSENBACH, C. W.: Unpublished data.
30. STEARNS, W. H., DRINKER, C. K., and SHAUGHNESSY, T. D.: The electrocardiographic changes found in 22 cases of carbon monoxide poisoning, *Am. Heart Jr.*, 1938, xv, 434-447.
31. STEWART, C. V., and MANNING, G. W.: A detailed analysis of the electrocardiogram of 500 RCAF Air Crew, *Am. Heart Jr.*, 1944, xxvii, 502-523.
32. THOMPSON, W. D.: The electrocardiogram in the hyperventilation syndrome, *Am. Heart Jr.*, 1943, xxv, 372-390.
33. WENDKOS, M. H.: The influence of autonomic imbalance on the human electrocardiogram. I. Unstable T-waves in precordial leads from emotionally unstable persons without organic heart disease, *Am. Heart Jr.*, 1944, xxviii, 549-567.

RENAL CHANGES IN SECONDARY SHOCK*

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RECENT medical literature contains numerous contributions on a clinico-pathological entity affecting primarily the kidneys and variously called toxic nephritis (Brown, Eusterman, Hartman and Rowntree¹), hepato-renal syndrome (Helwig and Schultz²), nephrosis (Wilbur³), clinically acute nephritis (Bell⁴), acute hematogenous interstitial nephritis (Kimmelstiel⁵), extra renal azotemia (Jeghers and Bakst⁶), acute interstitial nephritis (Melnick⁷), crush syndrome (Bywaters⁸) and so forth. Clinically the syndrome is characterized by either a sudden and obvious onset accompanied by some or all of the manifestations of peripheral vascular collapse, or by a more insidious and imperceptible origin. In either case there is frequently hemoconcentration, a drop in blood pressure, and gradually increasing oliguria ending in anuria and death in uremia. Pathologically the kidneys are usually enlarged, congested, show some obscuring of the corticomedullary demarcations, an eversion of the cut edges and swollen cortices. Microscopically the glomeruli are either normal or congested and contain edema fluid. The tubules are dilated. Their epithelial cells show various degrees of degeneration to complete necrosis and occasionally regeneration and the lumina contain hemoglobin, hyalin or cellular casts. The interstitial tissue is edematous and often infiltrated with plasma cells, lymphocytes and polymorphonuclear leukocytes.

Such a syndrome has been described in a wide variety of clinical disorders some of which are (1) severe infections as peritonitis, septicemia, abscess, pneumonia, etc.,^{9, 10, 11} (2) as a result of transfusion reactions,^{10, 11, 12, 13} (3) post operatively,⁶ (4) intestinal obstruction,^{1, 14} (5) crushing injuries,^{8, 15} (6) a variety of liver disturbances accompanied or unaccompanied by jaundice,^{16, 17, 3, 18, 19} and (7) various unrelated chemicals including the sulfonamides,^{20, 21, 32} bichloride of mercury,^{2, 22} carbon tetrachloride,²³ iodides,⁶ quinine,²⁴ and cantharidine.²⁵ Although it is thus apparent that the causes of the syndrome are protean, and that therefore the exact mechanisms involved as expressed by the different authors may also vary, it has perhaps not been generally realized that the one denominator common to many of the cases, regardless of whether the disorder arises abruptly or whether its onset is more insidious, is peripheral vascular collapse or better known as shock.

It is the purpose of this communication to present a group of selected cases representing a wide variety of disease processes that showed the typical clinical and pathological picture of the syndrome as related above, and in which the phenomenon of shock was observed either early in the last

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illness or shortly before death. These cases were selected from approximately the last 1500 necropsies performed at the Jefferson Medical College Hospital covering a period of five years. They represent only a portion of the total number of cases of the syndrome encountered and were selected to show the divergent conditions under which both the syndrome and the phenomenon of shock occur rather than to indicate their frequency.

CASE REPORTS

Case 1. Reaction to Transfusion of Incompatible Blood. A colored woman 36 years old was admitted to the hospital with pneumonia for which she was given a course of sulfonamides for four days. At this time the sulfonamide blood level was 2.3 mg. per 100 c.c. Twelve days after admission she was given by mistake 75 to 100 c.c. of citrated blood of the wrong blood group. There was no immediate reaction but eight hours later her temperature rose to 102° F. and she developed a headache and passed dark brown to black urine. Subsequently she vomited and in a few days developed repeated convulsions. She died in pulmonary edema and severe oliguria seven days after the transfusion. The pertinent laboratory data were as follows: before the transfusion erythrocytes 2,290,000 per cu. mm. and hemoglobin 39.2 per cent whereas the day following the transfusion they were 3,580,000 per cu. mm. and 46.5 per cent respectively: a gradual increase of the blood urea nitrogen and creatinine from normal to 35.2 mg. per 100 c.c. and 6 mg. per 100 c.c. respectively three days before death: following the transfusion persistent high specific gravity, albumin, pus cells, erythrocytes and casts in the urine: a normal fluid intake and output before the transfusion whereas subsequently a fluid intake on successive days of 2275, 2280, 2300, 6000, 5000 and 4600 c.c. with a corresponding urine output of 35,850, none, 30, 75, and 85 c.c.: a normal blood pressure throughout.

Necropsy was performed 11 hours after death. There was no jaundice. The subcutaneous tissue throughout the body contained edema fluid and in addition each pleural and the peritoneal cavity contained 1200 c.c. of clear fluid. The right lung weighed 960 gm. and the left one 800 gm. Each showed marked edema. The spleen weighed 240 gm.; the liver 2000 gm. and each kidney 220 gm. The capsules of the kidneys were slightly adherent to the cortices. Cut surfaces showed congested, swollen cortices, slightly obscured corticomedullary junctions, an eversion of the cut edges and edema of the peripelvic fat and connective tissue.

Microscopically the kidneys showed the changes typical of transfusion reactions. They consisted of relatively normal glomeruli except for congestion and edema of the tufts and often precipitated pink granular material in Bowman's spaces. The proximal convoluted tubules showed marked degeneration of the epithelium with occasional complete necrosis and sloughing, and dilated lumina often filled with precipitated pink staining material. The epithelial cells of the loops of Henle were normally intact but their lumina contained "hemoglobin," erythrocytes, or hyalin casts. Changes in the distal convoluted tubules were the same as those in the proximal ones except that they were less severe and occasionally their lumina contained casts similar to those found in Henle's loops. The interstitial connective tissue disclosed marked edema, engorgement of the capillaries with erythrocytes and scattered lymphocytes, plasma cells and eosinophiles. The collecting tubules showed various types of casts. Microscopic sections of the lungs showed diffuse congestion and edema with early terminal pneumonia. The liver disclosed marked congestion of the sinusoids and edema of the perisinusoidal spaces. There were no other contributory findings.

Case 2. Perforated Cholecystitis and Bile Peritonitis. A white man 55 years old was admitted in a state of prostration with a history of severe epigastric pain and

nausea and vomiting of 24 hours' duration. Operation the following day disclosed a perforated gall-bladder and bile in the peritoneal cavity. The next day he became comatose and remained in this state until death four days later. During his illness the temperature varied between 100° F., and 106° F., and the blood pressure before and after operation between 100 to 140 mm. Hg systolic and 68 to 90 mm. Hg diastolic. During the operation, however, it was 60 to 78 mm. Hg systolic and 50 or not obtainable diastolic for two and one-half consecutive hours. The blood non-protein nitrogen was 70 mg. per 100 c.c. on the day of operation and 150 mg. three days later. The erythrocytes numbered 4,150,000 per cu. mm. the day after operation and 5,600,000 per cu. mm. two days later. On the day of operation and on each subsequent day the fluid intake was 3000 c.c., 2000 c.c., 3000 c.c., 2000 c.c., and 3500 c.c. and the corresponding urinary output was 80 c.c., 100 c.c., 50 c.c., 900 c.c. and 2100 c.c. One recorded urinalysis on admission showed an acid reaction, specific gravity of 1.027 and a cloud of albumin.

Necropsy was performed three hours after death. The peritoneal cavity did not contain bile nor did it show any peritonitis. The gall-bladder was thick, firm, edematous and its tip contained a drain. There was no biliary obstruction and the liver was normal. The left kidney weighed 270 gm. and the right 190 gm. The capsules were adherent and the cortices, dull, rough, reddish brown and irregularly congested. Cut surfaces showed swollen cortices, an eversion of the edges and some obscuring of the corticomedullary demarcations. The perirenal tissue on the right side was indurated, hemorrhagic and showed areas of fat necrosis measuring as much as 5 cm. across. The pancreas was normal. The spleen weighed 350 gm. Permission to examine the thoracic organs was not granted.

Microscopic sections of the kidneys showed the same changes as in Case 1 except that there was more congestion and edema of both the glomeruli and interstitial connective tissue; less degeneration and more dilatation of the convoluted tubules; fewer foci of inflammatory cells, and occasional completely hyalinized glomeruli. The gall-bladder wall was edematous and diffusely infiltrated with plasma cells, lymphocytes and polymorphonuclear leukocytes. Sections of the remaining abdominal organs showed no contributory findings.

Case 3. Ulcerative Esophagitis, Enteritis and Colitis. A white woman 63 years old was admitted with a history of constipation and diarrhea for five years; periodic bouts of nausea and vomiting with poor appetite for three years; belching of gas and hiccoughs for three months and tarry stools for one week. The abdomen became distended 24 hours after admission and with this she became progressively weaker and died 7 days later. The blood pressure was 140 mm. of Hg systolic and 80 mm. of Hg diastolic on admission, but it gradually declined until the day before death it was 80 mm. Hg systolic and 50 mm. diastolic and several hours before death 66 mm. Hg systolic and 44 mm. diastolic. The last erythrocyte count obtained four days before death was 3,000,000 per cu. mm. Previous ones were essentially similar. The non-protein nitrogen level of the blood first taken three days after hospitalization was 286 mg. per 100 c.c. whereas on the day before death it was 192 mg. The daily intake of fluids varied from 2500 c.c. to 3000 c.c. and the corresponding urinary output from 550 c.c. to 1000 c.c. A urinalysis one day before death showed an acid reaction, a specific gravity of 1.011, a cloud of albumin and 10 to 20 pus cells per high power field. The serum van den Bergh was negative.

Necropsy was performed nine hours after death. Each pleural cavity contained an "excess" of serous fluid. The right lung weighed 510 gm. and the left one weighed 410 gm. Cut surfaces of each disclosed congestion and edema. The mucosa of the esophagus, jejunum, cecum and ascending colon contained numerous ulcers that measured as much as 1 cm. across. The mucosa of the jejunum showed in addition a gray pseudomembrane covering the nonulcerated portions. Congestion was

patchy. The right kidney weighed 200 gm. and the left 180 gm. Grossly they were essentially normal. The spleen weighed 90 gm. The remaining organs were normal.

Microscopic sections of the kidneys disclosed marked degeneration of the epithelial cells of the convoluted tubules, especially the proximal ones. Their lumina were markedly dilated and contained pink staining precipitated material and less frequently erythrocytes. Hyalin or "hemoglobin" casts were particularly abundant in the loops of Henle where the epithelial cells were well preserved. They were less frequently present in the distal convoluted tubules. The epithelium of the collecting tubules was undisturbed. Their lumina contained various types of casts. The supporting connective tissue of the cortex showed marked edema, congestion of the capillaries and focal collections of plasma cells and lymphocytes. The glomeruli were congested. Sections of the esophagus, jejunum and colon showed acute nonspecific ulcers with marked congestion of the submucosal capillaries. The lungs disclosed marked congestion and less edema. Sinusoidal congestion and perisinusoidal edema of the liver with compression of the liver cells were severe. Sections of the remaining organs disclosed no contributory findings.

Case 4. Pneumonia. A white man 58 years old was admitted in "an extreme state of cardiac collapse." He was orthopneic, irrational, and examination disclosed bubbling râles in his lungs and trachea, and edema of the ankles. He died one and one-half hours after admission. The erythrocytes numbered 5,000,000 per cu. mm. The hemoglobin was 86 per cent and the white corpuscles numbered 9200 per cu. mm. The blood pressure was 180 mm. Hg systolic and 105 mm. diastolic. The pulse was 130, temperature 102.4° F. and the respirations 50 per minute.

Necropsy was performed 12 hours after death. There were 100 c.c. of fibrinopurulent exudate in the left pleural cavity. The left lung weighed 890 gm. and the right one 480 gm. An acute pneumonic process completely replaced the left upper lobe while throughout the left lower lobe and the entire right lung there was an excess of serosanguineous fluid. The left kidney weighed 230 gm., the right 160 gm., and the spleen 160 gm. Both the kidneys and the spleen were grossly normal.

Microscopically there was severe congestion of the renal glomeruli and interstitial connective tissue. Edema was marked in the latter but only slight in the former. Foci of inflammatory cells were not seen. The epithelial cells of the convoluted tubules were so swollen and granular that the lumina were completely or almost completely occluded. In addition some of the cells were cast off and filled either the same or most distal portions of the tubules. There was no epithelial regeneration. Henle's loops were usually normal, and while the epithelium of the collecting tubules was intact, their lumina contained cellular, hyaline or "hemoglobin" casts. Throughout the liver there were foci of intense congestion and extravasation of blood and plasma. The lungs showed congestion, edema and extensive pneumonia.

Case 5. Intestinal Obstruction and Localized Peritonitis. A colored man, 41 years old, was admitted with severe epigastric pain of one day's duration and nausea and vomiting of a few hours' duration. Six days later he was operated upon for intestinal obstruction at which time a portion of the small bowel was resected. Following the operation dark fluid continued to be extracted through the Wangenstein tube. Five days postoperatively his sclerae became icteric and he died 24 hours later. During the operation the blood pressure was so low that it was not obtainable for 40 consecutive minutes. Subsequently it rose to 98 mm. of Hg systolic and 60 mm. diastolic. A single blood count taken four days after admission showed 5,250,000 erythrocytes per cu. mm.; 106 per cent hemoglobin and 7200 white blood corpuscles per cu. mm. The blood non-protein nitrogen and creatinine rose from normal on admission to 74 mg. and 3.58 mg. per 100 c.c., respectively, two days before death. The daily fluid intake varied from 3000 c.c. to 4000 c.c. and the urinary output from

600 to 1800 c.c. The urine was consistently amber to black and showed a specific gravity of 1.009 to 1.029 and the presence of albumin.

Necropsy disclosed icterus of the skin and mucous membranes. The abdomen was distended and the peritoneal cavity showed both acute localized peritonitis and abscesses. Each kidney weighed approximately 250 gm. The capsules were adherent and the external surfaces were rough and yellowish brown. Cut surfaces showed swollen cortices and everted edges. The right and left lungs weighed 660 gm. and 330 gm. respectively. The spleen weighed 230 gm. and the liver 2080 gm. Both these and the remaining organs were grossly normal.

Microscopically the kidneys showed the same changes as previously described. Degeneration of the proximal convoluted tubules was marked, and their lumina were dilated and filled with pink staining precipitated material. The epithelium of the loops of Henle was uninvolved while that of the distal convoluted tubules showed some degeneration but less than that in the proximal segments. "Hemoglobin," hyaline and cellular casts were prominent in both the loops of Henle and the distal convoluted tubules as well as the collecting tubules. The liver showed congestion of the sinusoids, edema of the perisinusoidal spaces and a diffuse sprinkling with polymorphonuclear leukocytes. The submucosa of the intestine showed marked capillary congestion and edema.

Case 6. Subdiaphragmatic Abscess. A colored man 47 years old was admitted with pain in the upper abdomen, vomiting and weakness of 12 hours' duration. He was restless and his skin was cold, wet and clammy. His temperature was 100° F. and his blood pressure was 60 mm. Hg systolic and 50 mm. diastolic. Although with treatment he reacted satisfactorily, he subsequently had repeated chills, fever and vomiting and died in pulmonary edema 30 days after admission. One day after admission the erythrocytes numbered 5,630,000 per cu. mm. and the hemoglobin was 90 per cent. The next day the erythrocytes numbered 5,200,000 per cu. mm. and the hemoglobin was 86 per cent whereas the remaining counts averaged 3,550,000 per cu. mm. and 77 per cent respectively. Five days before death the blood non-protein nitrogen was 63 mg. per 100 c.c. and the creatinine was 2.7 mg. per 100 c.c. The daily intake of fluids varied between 1840 c.c. and 6000 c.c. while the urinary output varied between 700 c.c. and 3800 c.c. Urinalysis showed a specific gravity about 1.013, albumin 1+ to 3+ and few to many pus corpuscles.

Necropsy performed five hours after death was confined to the abdomen. The peritoneal cavity was normal, but in the left upper quadrant there was a localized subdiaphragmatic abscess containing 100 c.c. of grayish yellow pus and walled off by the spleen, stomach, diaphragm and liver. Each kidney weighed 280 gm. The capsules stripped easily leaving smooth surfaces. Cut surfaces disclosed edema of the cortices and everted edges but were otherwise normal. The spleen weighed 350 gm. and the liver 2450 gm. All the abdominal organs appeared somewhat icteric.

Microscopically the renal changes, as in the cases above, disclosed moderate degeneration of the tubular epithelium; marked tubular dilatation; precipitated granular material in all the tubules; granular casts in the Henle's loops, distal convoluted tubules and collecting tubules and in the latter also hyaline casts; marked congestion and edema of the interstitial connective tissue with foci of lymphocytes and plasma cells, and congestion of the glomeruli. Sections through the abscess wall showed granulation and fibrous tissue infiltrated with a variety of cells of inflammatory origin. There were congestion and edema of the omentum, pancreas and liver and congestion of the spleen.

Case 7. Extensive Burns. A white man, 53 years old, was admitted in a state of severe shock with extensive burns of the face, hands, abdomen and extremities. With treatment he gradually recovered from the acute symptoms and was making satisfactory progress until 32 days after admission when he gradually developed

pulmonary edema, a decline in blood pressure to 50 mm. Hg systolic and 20 mm. diastolic, became stuporous and died two days later. On the day of admission the erythrocytes numbered 6,330,000 per cu. mm. and the following day 5,380,000 per cu. mm., while subsequently they dropped to an average of 3,000,000 per cu. mm. The daily fluid intake varied from 3500 c.c. to 5500 c.c. and the urinary output from 500 c.c. to 4550 c.c. The specific gravity of the urine varied from 1.010 to 1.026 and it consistently showed albumin but was otherwise negative. The non-protein nitrogen was normal until two days before death when the level was 52 mg. per 100 c.c.

Necropsy was performed 14 hours after death. The burned areas of the skin were covered with both crusts and purulent material. There was generalized subcutaneous edema. The left kidney weighed 320 gm. and the right 210 gm. The capsules were not adherent. The cortices were swollen and the cut edges were everted. The left lung weighed 630 gm. and the right 850 gm. Each showed increased crepitations and upon section a marked increase of serosanguineous fluid but no pneumonia. There were severe patchy congestion throughout the intestines and superficial erosions in the duodenum. The spleen weighed 260 gm. and the liver 2050 gm.

Microscopic sections of the kidneys disclosed complete necrosis and swelling of the epithelial cells of the proximal convoluted tubules to such a degree that the lumina were completely occluded. The epithelial cells of Henle's loops were relatively well preserved while those of the distal convoluted tubules showed marked degeneration but were better preserved than those of the proximal convoluted tubules. The collecting tubules contained scattered "hemoglobin" and hyalin casts. The glomeruli were congested. The interstitial tissue showed marked congestion of the lungs, liver and submucosa of the small intestine, and edema of the lungs, liver, corium, and testes.

Case 8. Hodgkin's Disease with Massive Necrosis of Involved Organs. A white man, 49 years old, was known to have Hodgkin's disease for two months during which time he was given deep roentgen-ray therapy. He returned to the hospital with constipation, fever, nausea and vomiting, headache and tired feeling. Deep therapy was continued until death two weeks after admission. Four blood counts disclosed an average of 3,200,000 erythrocytes per cu. mm. and a hemoglobin of 61 per cent. The daily fluid intake varied from 1390 c.c. to 1660 c.c. and the urinary output from 550 c.c. to 750 c.c. The blood pressure readings in mm. of Hg on the following days after admission were: first 80/60; second 80/60; seventh 110/60; eighth 72/50; ninth 80/56; eleventh 70/50; twelfth 60/? and thirteenth 110/70.

Necropsy was performed 17 hours after death. The body was emaciated and jaundiced. Lymph nodes in the left side of the neck, the left inguinal region, mediastinum, along the abdominal aorta and in the left lower quadrant were enlarged to as much as 10 cm. in diameter. They were firm, matted, and on section disclosed yellowish gray tissue. The liver weighed 2540 gm. and the spleen 210 gm. Each contained yellow tumor masses measuring from 1 to 6 cm. across. Each kidney weighed 160 gm. The capsules were not adherent and the external surfaces were dark red and somewhat granular. Cut surfaces were essentially normal. The left lung weighed 510 gm. and the right 610 gm. Excessive frothy serosanguineous fluid was found both within the lungs and in the trachea and bronchi. Microscopic changes in the kidneys were identical with those in the cases already described. Congestion and edema of both the glomeruli and interstitial connective tissue were particularly prominent. Numerous sections taken from the tumor masses described above besides showing a cellular infiltration typical of Hodgkin's disease disclosed massive complete necrosis of approximately three-quarters of the total tumor tissue. Capillo-venous congestion and interstitial edema were particularly conspicuous in the lungs, myocardium and liver.

Case 9. Obstructive Jaundice Caused by Carcinoma of the Pancreas. A white

man, 70 years old, was admitted with pain in the right upper quadrant and jaundice of three weeks' duration. The gall-bladder was large and tender. Three days after admission a cholecystojejunostomy was performed following which the jaundice increased in severity, the urine became almost black and he died in coma on the seventh postoperative day. Before operation the erythrocytes numbered 3,800,000 per cu. mm. and the hemoglobin was 78 per cent; two days after operation they numbered 5,500,000 per cu. mm. and the hemoglobin was 118 per cent; four days after operation the erythrocyte count was 5,000,000 and the hemoglobin 97 per cent. Two days before death the blood urea N was 24.4 mg. per 100 c.c. and the creatinine was 2.25 mg. per 100 c.c. The daily intake of fluids varied between 2360 c.c. and 3360 c.c., and the urinary output varied between 1700 c.c. and 3100 c.c. The urine was brown to black; acid in reaction; specific gravity 1.016 to 1.020; albumin present and many pus corpuscles. The systolic blood pressure varied from 100 to 150 mm. Hg and the diastolic was around 70 mm. Hg.

Necropsy was performed six hours after death. There was extreme jaundice. The head of the pancreas was replaced with a carcinoma 6 cm. in diameter and this partially compressed the common bile duct. The cholecystojejunostomy was patent but contained no bile for the common hepatic duct was by mistake completely ligated. There was much dilatation of the biliary tree above the point of ligation and severe jaundice of the liver. The left kidney weighed 180 gm. and the right 220 gm. Except for being jaundiced they were essentially normal. The spleen weighed 240 gm. Each lung showed increased crepitations and on section marked diffuse congestion and edema, and pneumonia in the dependent portions. The mucosa of the tracheo-bronchial tree was congested and the lumen contained frothy fluid.

Microscopic changes in the kidneys were similar to those previously described. Capillo-venous congestion and edema of the glomeruli and interstitial tissue were marked. Degeneration of the proximal convoluted tubules was more marked than of the distal ones, but both were dilated. "Hemoglobin" and hyaline casts were present in the lower nephrons. Sections of the pancreas disclosed an adenocarcinoma. In the liver sinusoidal congestion, perisinusoidal edema and precipitated bile pigment were prominent. The lungs disclosed congestion, edema, and terminal pneumonia.

Case 10. Bichloride of Mercury Poisoning. A white man, 50 years old, was admitted to the hospital four hours after he had swallowed five bichloride of mercury tablets. Before admission he had vomited bile and had several bloody bowel movements. Early the following morning he was in a state of shock. His skin was cold, clammy and disclosed beads of perspiration. The pulse could not be obtained; râles developed at both bases of the lungs; dyspnea set in, and he died in pulmonary edema 14 hours after admission. The erythrocytes numbered 5,750,000 per cu. mm. and the hemoglobin was 90 per cent. A few drops of urine obtained by catheter showed 5 to 10 pus cells per high power field but no other abnormalities. The blood non-protein nitrogen was 38.12 mg. per 100 c.c. and the blood pressure was not recorded.

Necropsy was performed four hours after death. There were slight edema of the tibia and cyanosis of the face and fingers. Superficial burns were present in the mouth, lips and tongue whereas in the esophagus, stomach and small intestine there were superficial ulcers and intense congestion of the mucosa. The stomach contained 300 c.c. of thick bloody fluid and the peritoneal cavity about 500 c.c. of watery blood tinged fluid. Each lung weighed 420 gm. and disclosed an excess of frothy fluid. The spleen weighed 240 gm. Each kidney weighed 170 gm. They were brownish red, and from the cut surface there oozed a considerable amount of blood.

Microscopically the kidneys showed complete necrosis and sloughing of the epithelium of the proximal convoluted tubules with complete occlusions of the lumina. The epithelial cells of the lower nephron exhibited only slight degeneration, and the

collecting tubules contained erythrocytes. There was severe congestion of the capillaries of the glomeruli and interstitial connective tissue. Congestion was so marked in the mucosa and submucosa of the esophagus, stomach and intestine as to border on infarction. Congestion and edema of the liver were less intense and more marked in the center of the lobules.

Case 11. Arsphenamine Poisoning. A white woman, 35 years old, received an intravenous injection of 0.3 gm. of arsphenamine and in a few minutes developed hot flashes and dyspnea. Within two hours the dyspnea increased, and there appeared chills, sweats, nausea and vomiting, aching in the extremities and lower spine and cyanosis. Next day icterus appeared and this deepened until she died in coma 10 days after the injection. On admission to the hospital the blood pressure was 90 mm. Hg systolic and 60 mm. diastolic, but on subsequent days rose to as much as 170 mm. Hg systolic and 90 mm. diastolic. The first erythrocyte count and hemoglobin, recorded two days after admission, were 3,100,000 per cu. mm. and 60 per cent respectively, whereas on subsequent examination the erythrocytes numbered as low as 1,650,000 per cu. mm. and the hemoglobin was 35 per cent. In the first 24 hours after injection she excreted only 250 c.c. of mahogany brown urine. The subsequent urine output in 24 hours varied between 200 c.c. and 900 c.c. while the intake of fluids ranged from 2700 c.c. to 4000 c.c. Repeated urinalysis disclosed specific gravity of 1.010 to 1.016, albumin, erythrocytes, pus cells and granular casts. The blood non-protein nitrogen and creatinine gradually rose to 193 mg. and 10.3 mg. per 100 c.c. respectively.

Necropsy was performed two hours after death. There was jaundice and generalized subcutaneous edema. Each pleural cavity contained 2000 c.c. of blood tinged fluid. The left lung weighed 420 gm. and the right 510 gm. The parenchyma, bronchi and trachea contained a great amount of bloody frothy fluid. Each kidney weighed 415 gm. The external surfaces were smooth and showed scattered petechiae. Cut surfaces revealed swollen cortices, obscured demarcations and considerable congestion. The spleen weighed 240 gm. and the liver 2200 gm. The gall-bladder wall was edematous.

Microscopically the proximal and distal convoluted tubules of the kidney could not be distinguished for all were greatly dilated and lined with greatly flattened and attenuated epithelium. Casts composed of erythrocytes, pus cells, epithelial cells and amorphous material were found in all tubules but were particularly abundant in Henle's loops and collecting tubules. The glomeruli were congested and Bowman's spaces were dilated. The interstitial tissue showed congestion, edema and scattered collections of plasma cells and lymphocytes. The liver cells were degenerated in patchy areas but, throughout, both they and the bile canaliculi contained an abundant amount of bile. The sinusoids were congested. The lungs showed congestion, edema and terminal pneumonia. The bone marrow was active.

Case 12. Diffuse Hepatic Necrosis Caused by Sensitivity to Sulfadiazine. A white woman, 45 years old, was in the hospital one month previously for a hysterectomy at which time she received 4 gm. of sulfadiazine daily for four days. Because she now developed chills, fever and pain in the back she was thought to have pyelitis and so was given a total of 6 gm. of sulfadiazine. Another 3 gm. was administered after she entered the hospital at which time she developed a sharp rise in temperature and a generalized macular rash. The sulfonamide level of the blood at this time was 6.7 mg. Within the next 24 hours she became stuporous, developed twitchings of the facial muscles, then convulsions and jaundice and died in coma two days after the sulfadiazine was discontinued. Before she died 500 c.c. of bloody fluid were aspirated from the stomach and a statement was made that in the last few hours of her life she was "in a state of shock." Two days before death the blood non-protein nitrogen was 62.5 mg. per 100 c.c. and the creatinine 2.11 mg. per 100 c.c.

The urine showed a specific gravity of 1.007 and both albumin and granular casts. The blood pressure was normal and on the day of death the erythrocytes numbered 4,300,000 per cu. mm. and the hemoglobin was 75 per cent.

Necropsy was performed nine hours after death. Each pleural cavity contained 100 c.c. and the peritoneal cavity 1000 c.c. of light brown fluid. Although the right lung weighed only 300 gm. and the left 210 gm. serosanguineous fluid within the parenchyma was in excess of normal and the lumen of the tracheobronchial tree contained frothy fluid. Each kidney weighed 210 gm. The capsules were not adherent. Cut surfaces showed sharp demarcations and swollen, pale, reddish brown cortices. Both pelves and ureters were normal, showing no signs of either hydro-nephrosis or infection. The liver weighed 1450 gm. It was soft and flabby. Cut surfaces were smooth and dull yellowish brown with numerous dark red hemorrhagic foci in the central portion. The spleen weighed 300 gm.

As in the previous cases the kidneys microscopically showed severe degeneration of the proximal convoluted tubules with only moderate changes in the distal ones. The lumina of the proximal tubules that were patent contained precipitated granular material whereas those of the entire lower nephron contained in addition hyaline and "hemoglobin" casts. There were marked congestion and edema of the glomeruli and interstitial connective tissue and in the latter, foci of plasma cells, lymphocytes and fewer polymorphonuclear leukocytes. Many sections of the liver showed a diffuse and complete necrosis of all the structures with irregular areas of hemorrhage. The lungs disclosed capillo-venous congestion and edema. The spleen was congested in spotty areas.

COMMENT

The criteria upon which the presence of the phenomena of shock was established in the cases reported here were those set forth by Moon.²⁶ In some instances the clinical findings were supported by both laboratory and necropsy examination, but when the laboratory data were incomplete, the clinical impression of the attending physician and the findings at autopsy constituted the basis for the diagnosis. More specifically, from the clinical and laboratory standpoints, case 1 developed a delayed reaction following a transfusion with a hemoconcentration of 1,290,000 erythrocytes per cu. mm. or 56 per cent of her normal, and finally died in pulmonary edema. Case 2 was admitted in prostration and for two and one-half consecutive hours during operation the blood pressure ranged from 68 to 90 mm. Hg systolic and 50 mm. Hg or not obtainable diastolic. Two days after operation there was a hemoconcentration of 1,450,000 erythrocytes per cu. mm. or 35 per cent, but because there was no record of an erythrocyte count before operation this, if anything, is a low estimate. In case 3 both the clinical and laboratory data were inconclusive, but the pathologic findings were typical of shock and will be considered below. Case 4 died before studies could be completed. It was stated, however, that he was admitted in an "extreme state of cardiac collapse" and pulmonary edema. His erythrocytes numbered 5,000,000 per cu. mm. and this probably represented a hemoconcentration. In case 5 for 40 consecutive minutes during the operation the blood pressure was so low that it could not be obtained. Only one blood count was recorded and it undoubtedly showed hemoconcentration for the erythrocytes numbered 5,250,000 per cu. mm. and the hemoglobin was 106

per cent. A third indication of shock was the extraction by way of the Wangensteen tube of darkly colored gastric fluid that was presumably partially digested blood. Case 6 on admission showed all the classic signs and symptoms of shock. The blood pressure was 60 mm. Hg systolic and 50 mm. diastolic and the first blood count taken 24 hours after admission disclosed 5,630,000 erythrocytes per cu. mm. If subsequent counts of 3,550,000 erythrocytes per cu. mm. could be taken as his normal there was a hemoconcentration of 2,080,000 or about 60 per cent. He died in pulmonary edema. Case 7 was admitted in shock with an erythrocyte count of 6,330,000 per cu. mm. Although his normal count was not known, there is nevertheless little doubt that this represented a hemoconcentration of at least 50 per cent. For two days before death his blood pressure was around 50 mm. Hg systolic and 20 mm. diastolic and he died in pulmonary edema. The only clinical manifestation of shock in case 8 was perhaps a blood pressure of 60 to 80 mm. of Hg systolic and not obtainable to 60 mm. of Hg diastolic for two weeks prior to death. In case 9 there was a postoperative hemoconcentration of 1,700,000 erythrocytes per cu. mm. or 44 per cent and an increase of hemoglobin from 78 per cent to 118 per cent. Case 10 besides showing the classic signs and symptoms of shock showed an erythrocyte count of 5,750,000 per cu. mm. which, because he was passing blood both in the stool and in the vomitus, represented a considerable hemoconcentration. The presence of the phenomenon of shock in case 11 was based upon the history of a reaction with a decline in blood pressure to 90 mm. Hg systolic and 60 mm. diastolic. Little can be said about hemoconcentration because an erythrocyte count was not done immediately. Finally, in case 12 the clinical data indicating shock were the history of a reaction, 500 c.c. of bloody fluid withdrawn from the stomach and the statement that preceding death the patient was in "a state of shock."

Both in experimental and clinical shock Moon²⁶ has described highly characteristic and constantly occurring pathologic changes. Fundamentally they consist of capillary atony due to injury of the endothelium, and are represented by dilated and engorged capillaries with extravasation of edema fluid and even erythrocytes into the adjoining parenchyma. While this change is almost always observed in the lungs it is also found fairly consistently in the liver, kidneys, gastrointestinal tract and other tissues. In addition, there is often an accumulation of serous or blood tinged fluid in the body cavities, frothy fluid in the tracheobronchial tree, terminal pneumonia, "coffee-ground material" in the stomach, and blood tinged mucus in the rest of the gastrointestinal tract. Although all the cases reported here showed various combinations of the above mentioned pathological changes, those most constantly observed were congestion and edema of the lungs, liver and kidneys and terminal pneumonia. Of special interest, perhaps, were the sinusoidal congestion and perisinusoidal edema so constantly seen in the liver, for these are in fact the changes seen in so-called serous hepatitis.

The morphologic changes in the kidneys in delayed lethal cases of acute

or incipient shock are so characteristic that a diagnosis can be highly suspected grossly and be made at a glance microscopically. The kidneys are usually enlarged. The capsules may or may not be adherent and the cortices are either smooth or granular. Cut surfaces show congestion, swollen cortices, an eversion of the edges, and sometimes obscured demarcations. Histologically the most striking changes are congestion and usually marked edema of the interstitial connective tissue with or without an infiltration of plasma cells, lymphocytes and less frequently polymorphonuclear leukocytes. There is severe degeneration to complete necrosis and even regeneration of the epithelial cells of the proximal convoluted tubules with relatively less degeneration of the distal convoluted tubules and still less or none at all of the lining cells of Henle's loops and the collecting tubules. Granular pink staining material is found in the proximal convoluted tubules and hyaline, "hemoglobin" or epithelial casts are present in the loops of Henle, the distal convoluted tubules and the collecting tubules. The glomeruli are usually congested and Bowman's spaces frequently contain edema fluid. Other renal changes that may be found are incidental.

Because of the widely divergent clinical conditions under which the renal changes as described can occur, it is quite evident that there is no single causative agent of the syndrome. Although certain substances, as for example bichloride of mercury,²⁸ are known to act directly upon the tubular cells of the kidney, they also cause destruction of other body tissues as for instance the mucosa of the intestines. It is highly probable that other chemicals may act solely by destroying body tissues with the liberation of protein or protein split products and that these in turn act upon the kidneys. One can in fact go a step further and say that any tissue poison be it a chemical, bacterium, toxin or trauma, which will cause tissue destruction with liberation of proteins or protein split products will thus indirectly produce the renal changes described above. These injurious agents may act either directly upon the tissues or indirectly by damaging the capillary endothelium and producing tissue anoxia. This is not a new concept for Hewitt⁹ in 1906 quotes Orth as saying that necrosis of the epithelium of the tubules can be produced by anemia of the tissues from various causes. Cooke and Whipple²⁷ in 1918 demonstrated in animals that a general toxic reaction with a rise in blood non-protein nitrogen is due not so much to the chemical agent or the bacteria as such, as it is to local cell injury or necrosis with the escape of toxic protein split products. Also experimentally Moon²⁶ has shown that one of the best methods of producing shock in dogs is the parenteral administration of ground tissues. This fact needs no better clinical support than the many excellent examples of shock and renal damage, as reported by Bywaters,⁸ that developed in patients with crushing injuries. Of the present series of cases the two best examples of production of the syndrome by tissue destruction are case 8 in which approximately three-fourths of the tumor tissue was completely necrotic, and case 12 in which there was complete necrosis of the liver.

Whereas in some cases functional renal changes are not striking, in others they are characteristic and consist of anuria or oliguria with often a highly colored urine, relatively high specific gravity, albumin, casts, erythrocytes and pus cells. These are accompanied by retention of nitrogenous waste products in the blood stream. The mechanisms responsible for these changes are undoubtedly many and rather complex. Jeghers and Bakst⁶ in their excellent article on extrarenal azotemia listed the causes of the syndrome under the following six headings: (1) a drop in blood pressure below the patient's normal, for it has been shown that as the systolic pressure drops the volume of urine decreases until a systolic pressure of 70 mm. Hg is reached when urine formation ceases entirely, (2) hypochloremia because of the concomitant loss of fluid and hyponatremia which produce a diminished blood plasma volume, (3) dehydration (which is accompanied by hemoconcentration), (4) liver damage with failure to synthesize the amino acids, (5) increased protein catabolism and (6) local renal disturbances consisting of changes in reabsorption activity of the tubules; control of the blood supply by afferent and efferent arterioles; stimulation of splanchnic nerves producing a decrease in the amount of urine secreted; rise in urine pressure in the intracapsular and tubular spaces due to blockage of the tubules; edema of the kidney substance producing an increase in the urine pressure, and hormonal control of renal function.

Although the above mentioned items appear to cover all the factors responsible for the functional derangement of the kidneys, there are a few points that need emphasis. The first is concerning the altered function of tubules when their epithelial cells are destroyed. In 1929 Richards²⁸ showed that by inhibiting the action of the tubular epithelium with mercury bichloride there was no urine secreted into the ureter and yet by actual measurement the glomerular filtrate was increased. His explanation was that the osmotic pressure of the blood proteins is unobstructed by the normal qualities of the tubular epithelium and is able to draw most of the glomerular filtrate back into the blood stream. If this is so when the blood is normal then it should be doubly so when there is hemoconcentration as is usually the case in shock.

Secondly, emphasis should be placed upon the interference with normal glomerular dynamics. In the normal human kidney Smith et al.²⁹ have shown that the effective glomerular pressure is the difference between the hydrostatic pressure in the efferent end of the glomerular capillary and such pressure distally as may oppose this pressure. The opposing pressure consists of (1) renal venous pressure which is normally negligible, (2) renal interstitial pressure and (3) the osmotic pressure of the blood. In shock there is (1) venous stagnation,^{30, 31} (2) an increase in the renal interstitial pressure due to edema and (3) hemoconcentration with an increase in the osmotic pressure of the blood. The net result is a total increase of the opposing pressure which with an already decreased head force³¹ due to a decline in the blood pressure reduces greatly the effective glomerular filtra-

tion, and this in turn diminishes the volume of urine secreted. This results in a retention of nitrogenous waste products in the blood stream.

Thirdly, it should be emphasized that the effective glomerular filtration pressure is further reduced in these cases of shock by an actual mechanical obstruction of the tubules, with an increase of tubular and capsular urine pressure. Tubular obstruction is accomplished by the formation of hyaline casts filling completely the lumina of the loops of Henle or of the more distally located tubules and the terrific swelling of the epithelial cells of particularly the proximal convoluted tubules. Tubular obstruction is manifested morphologically by (1) dilatation of the proximal convoluted tubules and Bowman's spaces sometimes to a marked degree, and (2) the accumulation of precipitated pink staining granular material in the same locations.

It is the rule rather than the exception that in this syndrome the specific gravity of the urine is relatively high in spite of the apparent renal insufficiency. This can be accounted for by the morphological changes in the kidneys. The glomeruli are almost always intact, and so the glomerular filtrate although reduced as a result of altered glomerular dynamics, might still be of sufficient quantity to carry on the excretion of waste products if the tubular epithelium were intact, but since in all cases this shows degeneration to complete necrosis most of the filtrate is withdrawn back into the blood stream.²⁸ That which is left is further concentrated by the loops of Henle whose normal function it is to concentrate the urine and whose epithelial cells, in the cases presented here, were always relatively intact. That their function is unimpaired is supported by the fact that hyaline casts were found only in the loops of Henle and beyond—at the location where the water was removed and the protein sufficiently concentrated, and never in the proximal convoluted tubules where the filtrate was more dilute.

SUMMARY

Twelve cases of delayed death following acute or incipient shock produced by (1) a reaction to transfusion of incompatible blood, (2) perforated cholecystitis and bile peritonitis, (3) ulcerative esophagitis, enteritis and colitis, (4) pneumonia, (5) intestinal obstruction, (6) subdiaphragmatic abscess, (7) burns, (8) Hodgkin's disease with tissue necrosis, (9) obstructive jaundice, (10) bichloride of mercury poisoning, (11) neoarsphenamine poisoning and (12) diffuse hepatic necrosis caused by sulfadiazine are presented. Clinically there were varying degrees of oliguria, high specific gravity of the urine with albumin, casts, erythrocytes and pus cells, and a retention of non-protein nitrogen in the blood.

The pathologic changes in the kidneys are quite characteristic, and in the literature they have been described under a variety of names. Grossly the kidneys are enlarged and the capsules strip easily leaving smooth or finely granular surfaces. Cut surfaces show congested swollen cortices, an eversion of the edges, and sharp or slightly obscured corticomedullary demarca-

tions. Microscopically there are (1) congestion and edema of the interstitial connective tissue with or without cellular infiltration, (2) severe degeneration to complete necrosis of the epithelium of the proximal convoluted tubules with less degeneration of the distal convoluted tubules and still less or none at all of the lining cells of Henle's loops and collecting tubules, (3) granular pink staining material in the proximal tubules and various types of casts in the distal nephrons and (4) congestion and edema of the glomeruli.

Although the ultimate causes of the renal changes are divergent one denominator common to many of the cases is shock and, therefore, these changes are regarded as characteristic of this phenomenon.

BIBLIOGRAPHY

1. BROWN, G. E., EUSTERMAN, C. B., HARTMAN, H. R., and ROWNTREE, L. G.: Toxic nephritis in pyloric and duodenal obstruction, *Arch. Int. Med.*, 1923, xxxii, 425.
2. HELWIG, F. C., and SCHULTZ, C. B.: A liver kidney syndrome. Clinical, pathological and experimental studies, *Surg., Gynec. and Obst.*, 1932, lv, 1932.
3. WILBUR, D. L.: The renal glomerulus in various forms of nephrosis, *Arch. Path.*, 1934, xviii, 157.
4. BELL, E. T.: The pathology and pathogenesis of clinically acute nephritis, *Am. Jr. Path.*, 1937, xiii, 497.
5. KIMMELSTIEL, P.: Acute hematogenous interstitial nephritis, *Am. Jr. Path.*, 1938, xiv, 737.
6. JEGHERS, H., and BAKST, H. J.: The syndrome of extra renal azotemia, *Ann. Int. Med.*, 1938, xi, 1861.
7. MELNICK, P. J.: Acute interstitial nephritis with uremia, *Arch. Path.*, 1943, xxxvi, 499.
8. BYWATERS, E. G. L.: Ischemic muscle necrosis. Crushing injury, traumatic edema. The crush syndrome, traumatic anuria, compression syndrome. A type of injury seen in air raid casualties following burial beneath debris, *Jr. Am. Med. Assoc.*, 1944, cxxiv, 1103.
9. HEWITT, J. H.: Necrosis of epithelium in the kidneys in infections and intoxications, *Bull. Johns Hopkins Hosp.*, 1906, xvii, 272.
10. DE GOWIN, E. L., and BALBRIDGE, C. W.: Fatal anuria following blood transfusions. Inadequacy of present tests for compatibility, *Am. Jr. Med. Sci.*, 1935, clxxxviii, 555.
11. JOHNSON, R. A., and CONWAY, J. F.: Urinary suppression and uremia following transfusions of blood, *Am. Jr. Obst. and Gynec.*, 1933, cclxi, 255.
12. BORDLEY, J.: Reactions following transfusions of blood, with urinary suppression and uremia, *Arch. Int. Med.*, 1931, xlvii, 288.
13. DANIELS, W. B., LEONARD, W. B., and HOLTZMAN, S.: Renal insufficiency following transfusion. Report of 13 cases, *Jr. Am. Med. Assoc.*, 1941, cxvi, 1208.
14. ZEMAN, F. D., FRIEDMAN, W., and MAN, L. T.: Kidney changes in pyloric obstruction, *Proc. New York Path. Soc.*, 1924, xxiv, 41.
15. BYWATERS, E. G. L., and DIBLE, J. H.: The renal lesion in traumatic anuria, *Jr. Path. and Bact.*, 1942, liv, 111.
16. WILINSKY, A. O.: Occurrence, distribution and pathogenesis of so-called liver death and/or the hepatorenal syndrome, *Arch. Surg.*, 1939, xxxviii, 625.
17. AYER, D.: Renal lesions associated with deep jaundice with comments on their relations to those in the so-called hepatorenal syndrome and in transfusion reactions, *Arch. Path.*, 1940, xxx, 26.
18. LICHTMAN, S. S., and SOHVAL, A. R.: Clinical disorders with associated hepatic and

- renal manifestations with especial reference to the so-called hepatorenal syndrome, *Am. Jr. Digest. Dis. and Nutr.*, 1938, iv, 26.
19. SCHULTZ, C. B., and HELWIG, F. C.: A contribution to the study of so-called liver death, *Jr. Am. Med. Assoc.*, 1932, xcix, 633.
 20. SOBIN, S., ARONBERG, L. M., and ROLNICK, H. C.: The nature of the renal lesion with the sulfonamides and its prevention with urea, *Am. Jr. Path.*, 1943, xix, 211.
 21. MURPHY, F. D., KUZMA, J. F., POLLEY, T. Z., and GRILL, J.: Clinico-pathologic studies of renal damage due to sulfonamide compounds. A report of fourteen cases, *Arch. Int. Med.*, 1944, lxxiii, 433.
 22. HARMON, E. L.: Human mercuric chloride poisoning by intravenous injection, *Am. Jr. Path.*, 1928, iv, 321.
 23. SMETANA, H.: Nephrosis due to carbon tetrachloride, *Arch. Int. Med.*, 1939, lxiii, 760.
 24. TERPLAN, K. L., and JAVERT, C. T.: Fatal hemoglobinuria with uremia from quinine in early pregnancy, *Jr. Am. Med. Assoc.*, 1936, cvi, 529.
 25. OPIE, E. L.: Lymph formation and edema of the liver with experimental nephritis produced by cantharidin, *Jr. Exper. Med.*, 1912, xvi, 831.
 26. MOON, VIRGIL H.: Shock. Its dynamics, occurrence and management, 1942, Lea & Febiger, Philadelphia.
 27. COOKE, J. V., and WHIPPLE, G. H.: Proteose intoxication and injury of body protein. IV. The metabolism of dogs with sterile abscess, pancreatitis and pleuritis, *Jr. Exper. Med.*, 1918, xxviii, 223.
 28. RICHARDS, A. N.: Direct observations of change in function of the renal tubule caused by certain poisons, *Trans. Assoc. Am. Phys.*, 1929, xlv, 64.
 29. SMITH, H. W., CHASIS, H., GOLDRING, W., and RANGES, H. A.: Glomerular dynamics in the normal human kidney, *Jr. Clin. Invest.*, 1940, xix, 751.
 30. SMITH, H. W., ROVENSTINE, E. A., GOLDRING, W., CHASIS, H., and RANGES, H. A.: The effects of spinal anesthesia on the circulation in normal, unoperated man with reference to the autonomy of the arterioles and especially those of the renal circulation, *Jr. Clin. Invest.*, 1939, xviii, 319.
 31. COUNNAND, A., RILEY, R. L., BRADLEY, S. E., BREED, E. S., NOBLE, R. P., LAUSON, H. D., GREGERSEN, M. I., and RICHARDS, D. W.: Studies of the circulation in clinical shock, *Surgery*, 1943, xiii, 963.
 32. HERBUT, P. A., and SCARICACIOTOLLI, T. M.: Diffuse hepatic necrosis caused by sulfadiazine, *Arch. Path.*, 1945, xl, 94.

ACUTE MEDIASTINAL EMPHYSEMA *

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THE syndrome of acute mediastinal emphysema following trauma or pulmonary disease has been recognized for many years, but it is only recently that Hamman^{1, 2} has called attention to the spontaneous occurrence of this condition. Numerous case reports³⁻¹⁸ have been published following his description, but it is still regarded as a rare entity. Recently, moreover, reports of mediastinal emphysema secondary to other conditions have been less common than those of the spontaneous type. This subject is particularly important at the present time because many cases following trauma¹⁹ and influenzal pneumonia^{20, 21, 22} were reported during World War I and undoubtedly more cases have occurred during the present conflict. Cases in the United States Navy,¹⁸ United States Army,²³ and the Royal Canadian Air Force¹⁴ have already been reported. One of these occurred in an aviator who bailed out of an aeroplane after a mid-air collision¹⁸ and another in a soldier exposed to chlorine gas.²³ Lovelace and Hinshaw²⁴ have stressed the care with which all patients with chest injuries must be examined for signs of pneumothorax and mediastinal emphysema before embarking on aerial flights, in view of the marked increase in the pressure of air in closed cavities at high altitudes. We are reporting seven cases of mediastinal emphysema occurring in soldiers at an Army Air Force Technical School. One case was associated with an acute respiratory infection and bronchial asthma and subsequently developed an atypical pneumonia, while six were of the spontaneous type. Two of these cases are of special interest in that they ran a prolonged course, differing from the usual description of this syndrome.

Mediastinal emphysema has been described in association with many conditions. It occurs following trauma to the chest, either penetrating or non-penetrating, and with or without tension pneumothorax.^{19, 25} It has been reported following surgical procedures on the neck²⁶ and the thorax; following positive pressure anesthesia²⁷; after therapeutic pneumothorax²⁸ or traumatic or therapeutic pneumoperitoneum.²⁹ It occurs in association with acute infections, such as pneumonia,^{20, 21, 22, 30} influenza,³¹ diphtheria, and whooping cough, or severe coughing spells. It may occur with severe bronchial asthma^{32, 33} or tuberculosis,³⁴ or after exposure to pulmonary irritants.²³ It has been reported during labor and straining at stool, and it may occur in the newborn.^{37, 41} The clinical picture produced in association with these conditions differs not essentially from that arising spontaneously

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except that fatal cases have invariably occurred in the secondary group, and in this group clinical symptoms are apt to be more severe.

Pneumothorax occurs in many of these cases. It is usually small, occurring at either apex, more commonly on the left.² Unilateral or bilateral tension pneumothorax may result, however, especially in infants. The association of pneumothorax with mediastinal emphysema is so frequent that the presence of air in the mediastinum must be considered in all cases of pneumothorax. Hamman, especially, has pointed out this association and has suggested that the etiology of spontaneous pneumothorax may be mediastinal emphysema in a considerable proportion of cases.⁴³

MODE OF PRODUCTION

The possible mechanisms of production of mediastinal emphysema, with or without pneumothorax, may be summarized as follows. The primary source of the air in most cases is a ruptured alveolus or alveoli within the lung. Hamman² believes this is the mechanism in "spontaneous" cases. It may occur in normal lungs by extreme over-inflation, as has been demonstrated experimentally by Macklin,³⁸ Joannides and Tsoulos,³⁹ and Kelman,²² and as has presumably occurred clinically in those cases induced by positive pressure anesthesia,²⁷ those occurring in the second stage of labor,³⁵ and in some after tracheotomy.²⁶ It may occur in pathological lungs with weakened and distended alveolar walls, as has been observed following influenzal bronchopneumonia,^{20, 21} bronchial asthma^{32, 33} and congenital atelectasis.³⁶ Macklin³⁸ and Biering³⁶ have called attention to the importance of areas of atelectasis which stretch the surrounding alveoli and may cause easy rupture of the stretched alveolar membranes, allowing air access to the interstitial tissues. From the area of these ruptures, air may spread in two directions. It may spread to the periphery of the lung^{20, 21, 40} and form emphysematous blebs which may rupture and produce a pneumothorax; or subpleural air may dissect back to the pulmonary hilus and then into the mediastinum. Macklin³⁸ has shown experimentally that air from a ruptured alveolus can also move along the perivascular sheaths in the lung to the mediastinum and extend between the parietal pleura and pericardium.

From the mediastinum the air may spread in several directions. It may rupture the thin mediastinal pleura and produce a pneumothorax. Macklin has demonstrated that this method occurs in cats experimentally and it is probable that this is the mode of production of pneumothorax in the spontaneous cases. The air may also spread upward producing a subcutaneous emphysema of the neck,² even extending to the face³³ and downward over the chest wall. This is not an infrequent occurrence and is of course definite proof of the diagnosis of mediastinal emphysema. Air in the mediastinum has also been reported to dissect downward to the retroperitoneal tissues and even to the scrotum and perirectal tissues.¹⁶

There are other methods for the access of air to the mediastinum but

these are associated with trauma or surgical procedures. Air may be sucked directly into the mediastinum through wounds, such as those due to abdominal injuries or wounds of the neck. Wounds of the trachea or bronchi may also allow access of air to the mediastinum.²⁵

Macklin³⁸ feels that enough pressure can be produced by the air on the pulmonary vessels and pulmonary hilus to cause embarrassment to the circulation. Others have demonstrated collapse of the pulmonic and systemic veins.²⁵ Apparently, in the spontaneous cases reported thus far, the pressure of air in the mediastinum has not reached sufficient magnitude to produce circulatory obstruction, or else extension of the air to other tissues has relieved the pressure. In this connection, Torrey and Grosh²¹ observed marked relief of circulatory and respiratory embarrassment when subcutaneous emphysema appeared in their cases of influenzal pneumonia with pulmonary and mediastinal emphysema.

CLINICAL PICTURE

There are two outstanding features in the clinical picture of acute mediastinal emphysema: pain in the chest and a characteristic sound synchronous with the heart beat, described as crunching, bubbling, or clicking.¹² The pain is usually noted first in the left upper or midchest. It then becomes substernal and may radiate to the back, shoulder or arm, particularly the left arm. In many respects it closely simulates the pain of angina pectoris.³ It may be a severe, sharp, even agonizing pain. It is aggravated by motion, walking or movements of the trunk, and is somewhat relieved by rest. It is made worse by respiration and in this respect simulates acute pleurisy or acute pleurodynia. It may produce a guarded shallow type of breathing. After a variable period, in one of our cases approximately one hour, the patient may become aware of a crunching sound and sensation over the heart, more marked while leaning forward or lying on the left side. The pain may be aggravated by swallowing or turning the head. It usually subsides within a few hours and the patient is then quite comfortable, particularly if he remains quiet. The patient may prefer the recumbent position⁵ or a hunched over sitting position, as in two of our cases. Hyperesthesia of the skin over the precordium may be present.¹²

On physical examination the bizarre sounds heard over the precordium are diagnostic. They are caused by the heart contracting against bubbles of air lying between the parietal pericardium and the parietal pleura or within the mediastinal tissues or the lung. These sounds are difficult to describe accurately. Various adjectives have been used, any one or all of which may be applicable in any case. They may be described as clicking, crackling, crunching, creaking, bubbling, crushing, or popping. Cowart¹⁸ has compared them to the "sticky, popping sounds of noisily chewed gum." They are occasionally mistaken for a pericardial or pleuro-pericardial friction rub. They vary with respiration and may be completely obliterated in various

phases of the respiratory cycle. They vary also with the position of the patient, being most frequently audible with the patient lying on the left side. They may disappear on standing erect. After several hours they may disappear entirely but usually can be brought out again by mild exercise, such as sitting up in bed. The sounds may be heard over the whole precordium, or they may be localized to the region of the apex or to the midsternum. In one of our cases they disappeared from the apex but could still be heard over the upper sternum. The patient is usually aware of the sounds, not only feeling their vibrations but occasionally actually hearing the clicking as well. One patient described this sensation "as if gears were grinding together" in his chest.¹⁵ He even may feel them on swallowing.¹⁰ Occasionally they may be heard at a considerable distance from the patient. Frequently the sounds are palpable and have a short inconstant clicking sensation as distinct from the purr of a palpable vascular thrill. A phonocardiogram recorded in one case by Hoffman, Pobirs, and Merliss¹⁷ revealed the sounds to be synchronous with the cardiac impulse and occurring regularly with each cardiac contraction.

On percussion there may be no obvious change, but not infrequently there is diminution of cardiac dullness and even actual hyperresonance sub-sternally or over the heart. The magnitude of this change of course depends upon the amount and position of the mediastinal air. Within 24 hours, occasionally sooner, a subcutaneous emphysema may appear in the tissues of the neck. When present, this confirms the diagnosis.

When first seen the patient may be in mild shock due to the severity of the pain. In the spontaneous cases, however, this is usually not marked and is relieved by rest and sedation. There is usually no associated change in the pulse or blood pressure, no elevation of temperature, and no sign of venous obstruction. In the secondary type this may not be true, and the accumulation of air may be great enough to cause circulatory embarrassment with a picture similar to cardiac tamponade.

Careful physical examination of the chest may give the signs of a pneumothorax, but usually this is so small that it is not evident on examination.

Roentgen-ray examination of the chest may confirm the diagnosis.^{2, 4, 12, 41} Frequently there will be a thin line parallel to the cardiac border on either side or in only part of its extent, with an area of increased radiolucency between it and the heart. This line is due to air dissecting between the parietal pericardium and pleura and disappears with the absorption of the air. On oblique or lateral views small or large collections of air may be seen in the mediastinum. A helpful confirmatory finding is the frequent presence of a small pneumothorax, usually over the apex of the left lung. This also may be seen best in an oblique view. Occasionally a small pleural effusion may accompany the pneumothorax, as in our case 2.

Electrocardiograms show no distinctive changes. The white blood count may be moderately elevated but is usually normal. Sedimentation rates are within normal limits.

DIFFERENTIAL DIAGNOSIS

Difficulties in differential diagnosis should not be encountered in typical cases, once one is familiar with the bizarre sounds which occur over the precordium in this condition. There are two diseases most commonly confused with this picture—acute pericarditis and acute coronary occlusion with myocardial infarction. Acute pericarditis can be differentiated by the lack of fever and leukocytosis and the absence of electrocardiographic signs. The crunching, clicking sounds over the heart do not have the typical to-and-fro sound of a friction rub and once heard will not be confused with it. Acute coronary occlusion must be considered with the distribution of the pain. There are several factors, however, which are not found in coronary occlusion. The pain in coronary occlusion is not especially affected by respiration as it is in mediastinal emphysema. No sounds occur over the heart in coronary occlusion as occur in mediastinal emphysema. Fever, increased sedimentation rate, leukocytosis and electrocardiographic changes will finally serve to differentiate the two conditions. It must be remembered, however, that rarely there may be absence of pain or of the characteristic sounds. The patient may even walk about asymptomatic.

Greene¹³ has described knocking and tapping sounds over the heart in patients with a left pneumothorax. He did not hear the crunching, bubbling sounds typical of mediastinal emphysema, however, unless it was also present. He concluded that the "bubbling, crunching, clicking, and some of the tapping sounds" are due to the heart rubbing against emphysematous blebs in the lung and mediastinum. The knocking and tapping metallic sounds occurred only with a left pneumothorax with the heart striking a bleb over a partially collapsed lung or striking the diaphragm over a gas bubble in the splenic flexure of the colon. Our fifth patient presented both types of sounds over the precordium, and in this case the left pneumothorax was the largest in our group. Similar metallic sounds were heard by Smith⁴² and others in soldiers with wounds of the left chest in World War I. Unless one examines the patient in different positions to elicit the characteristic sounds, one may overlook them and miss the diagnosis completely or attribute all symptoms erroneously to the small associated pneumothorax. Hamman⁴³ has suggested that the etiology of spontaneous pneumothorax may be mediastinal emphysema in more cases than is usually considered.

TREATMENT

The treatment consists of bed rest. The patient usually is comfortable after resting a few hours, although analgesics or sedatives may be necessary. There is a definite tendency to recurrence. This has been noted among cases reported in the literature, and we noted it in five of our cases. We feel the patient should be kept at bed rest for several weeks until absorption of the air is complete and then allowed gradual return to full activity. In the

secondary cases with the symptoms of mediastinal obstruction with cyanosis, weak pulse, and dyspnea, it is possible that surgical incision in the supra-sternal notch would be necessary for evacuation of air and relief of pressure.⁴⁴ Incisions over the skin of the chest wall and direct aspiration of air with a needle have afforded relief from marked subcutaneous emphysema.³³

Acute cellulitis of the mediastinum as a result of mediastinal emphysema has not been reported, but it would appear to be a potential complication, particularly if there is an associated respiratory infection. In several of our cases we used sulfadiazine in small doses as a prophylactic measure. We feel that if respiratory infection is present, prophylactic chemotherapy is advisable to reduce the possibility of a dangerous mediastinal infection.

CASE REPORTS

Case 1. A 19 year old white male soldier was admitted on September 4, 1943, complaining of difficulty in breathing and a sore throat which was aggravated by successive bouts of coughing. The patient had begun to suffer from his annual attack of hay fever approximately three weeks prior to admission. Cough started on September 1, becoming productive of clear mucoid sputum within two days. On the day of admission his throat had become so sore and painful that he could no longer swallow food. Pain in the chest substernally, accentuated by coughing, first appeared on the evening of hospital admission and radiated upward into the neck anteriorly and bilaterally. There was no history of trauma or of sudden sharp pain in the chest. Physical examination on admission showed moderate nasal obstruction. There was exudate and marked diffuse injection of the posterior pharynx. There was extensive crepitation of air beneath the palpating fingers as well as exquisite tenderness in the supraclavicular areas and in the subcutaneous tissues of the neck bilaterally. There was a funnel-shaped depression of the sternum above the xiphoid cartilage. The respirations were labored and difficult. Percussion over the superior mediastinum yielded a tympanitic note and felt "spongy" to the palpating hand. Wheezes and râles of the asthmatic type were prominent over both lung fields, and tactile fremitus was generally increased.

Temperature was 99.6° F., pulse 90, respirations 22, blood pressure 124 mm. Hg systolic and 80 mm. diastolic. Laboratory data on admission were as follows: erythrocyte count 4,820,000 per cu. mm.; leukocyte count 9,450 per cu. mm.; hemoglobin 80 per cent; differential count normal. The urine was normal. Electrocardiogram was within normal limits. Roentgen-ray examination of the chest was normal on admission, but on the fifth hospital day revealed a small patch of pneumonia adjacent to the right heart border about 4 cm. in diameter and of a lobular distribution. No radiological evidence of pneumothorax was found. The heart shadow was not unusual. Subsequent films on the eleventh day showed migration of the lobular pneumonia to two new areas, one in the periphery of the right lower lobe and one in the right middle lobe. On the eighteenth day roentgen-ray examination showed regression of all three patches of pneumonia with parenchymal residua still present. The final examination one week later showed the lungs to be clear. The blood and urine examinations were repeated and found unchanged. Electrocardiogram on the twenty-first day showed no significant changes. Sputum showed no acid-fast bacilli throughout the hospital stay and no predominant organisms as a cause of the pneumonia. The subcutaneous crepitation gradually disappeared by the end of the first week at bed rest, though he continued to have slight pain in the right chest. He was dismissed after one month in the hospital with no positive findings remaining.

Comment. In this case, there were two factors which favored the development of interstitial pulmonary emphysema, the asthma and the acute respiratory infection. Possibly an early pneumonia, not demonstrable on the first roentgenogram, also was a contributing etiological factor. It is quite probable that the infection weakened the alveolar walls and the paroxysms of coughing and the asthma brought about the rupture of an alveolus.

Very probably, the patient's sore throat and difficulty in swallowing were as much related to the emphysema of the tissues as to the local infection in the throat. We classify this case as one secondary to respiratory infection and bronchial asthma.

Case 2. A 22 year old white male soldier was first admitted to the hospital on October 10, 1943 complaining of intermittent, sharp stabbing pain in the left anterior chest. Aside from a slight "head cold" without marked cough, of three weeks' duration, he was well until approximately 48 hours before admission when, while sitting still, he experienced a sharp stabbing pain in the precordium which radiated to the left shoulder and elbow and through to the back. The pain continued with variable intensity, was intensified by deep inspiration, and abated on bed rest.

The patient was well developed and well nourished and appeared to be in no acute distress at the time of admission. His temperature was 101.2° F., respirations 26 per minute, pulse 110 per minute, blood pressure 130 mm. Hg systolic and 90 mm. diastolic. The pharynx was slightly injected with a small patch of white exudate in the left tonsillar fossa. The lungs were clear on auscultation and percussion. The heart was not enlarged to percussion or palpation, there was a "palpable snap" in the third and fourth left intercostal spaces parasternally. The heart sounds were of good quality. The rhythm was regular. Loud "popping, scratching" sounds were heard in the third and fourth interspaces in both systole and diastole.

Leukocyte count on admission was 16,700 per cu. mm., five days later was 12,200 with 64 per cent polymorphonuclear leukocytes, and thereafter was normal. Sedimentation rates were normal. Throat culture revealed a non-hemolytic streptococcus. Several electrocardiograms at intervals of three to four days were within normal limits. Roentgenogram of the chest on admission showed a small left apical pneumothorax and slight clouding of the left costophrenic angle. Eight days later the air had been reabsorbed, but one week after that a small left pneumothorax, both apical and lateral, was again seen, along with a small amount of fluid in the left costophrenic angle. The pneumothorax did not again disappear until the twenty-seventh hospital day.

The temperature rose to 101.2° F. the day after admission, but he was afebrile for the remainder of his hospital stay. On bed rest the patient felt comfortable, but the peculiar precordial sounds continued to be heard for four weeks. During this time they frequently could be heard in the left lateral position. Occasionally they could be heard with the naked ear while standing at the bedside.

After 71 days, he was discharged home on a convalescent furlough for 15 days, but on January 7 had to be readmitted to the hospital because of a recurrence of sharp pain in the precordium with radiation to the back and left lateral chest wall. He stated that the pain had reappeared shortly after discharge from the hospital and had confined him to bed during most of his furlough. He had slight exertional dyspnea during this time. On admission physical examination was negative, as were further leukocyte counts, sedimentation rates, electrocardiograms, and roentgenograms of the chest. On the fourteenth hospital day, however, transient "scratchy" sounds, of the

same character as heard previously but of less intensity, were again heard. On the sixteenth day they were bubbly and popping and heard intermittently until patient's transfer to an Army General Hospital on January 28.

Except for the initial examination at the Army General Hospital, when a few "scratching to-and-fro" sounds were heard over the heart, no abnormal physical or laboratory findings were found. He was again discharged to duty on February 22 with a recommendation for light duty, not requiring strenuous physical exertion.

On March 7 he was again admitted complaining of left anterior and substernal chest pain of variable intensity, most marked on exertion. While in the hospital at bed rest the same characteristic sounds were heard transiently over the heart. These finally subsided again and the patient was discharged to duty on April 19.

Comment. At the outset, the patient presented the classic features of spontaneous mediastinal emphysema (except that his temperature and white blood cell count were elevated due to a mild upper respiratory infection), and it was expected that his convalescence would follow the same smooth course that all previously reported cases seemed to run. Despite four prolonged hospitalizations, however, the patient continued to complain of aches in the chest, and intermittently a few signs were heard over the heart which would seem to substantiate the fact that he was continuing to have mediastinal emphysema. It is possible that the process was in the nature of a "slow leak" rather than a repeated series of new accidents. At the present time, he is on limited duty.

Case 3. A 23 year old white male soldier was admitted May 5, 1944 complaining of severe pain in the left anterior chest. The past history and family history were non-contributory. He had had a mild respiratory infection with cough for two weeks. Suddenly, while walking, he had severe pain in the left anterior chest with numbness and pain in the left shoulder. The pain was accentuated by respiration. On examination he was perspiring, appeared frightened, and had difficulty breathing because of pain. Over the precordium were crackling, snapping sounds synchronous with the heart beat but varying with respiration and louder while lying on the left side. There was a palpable rub over the cardiac apex synchronous with the sounds. Percussion dullness was diminished over the sternum. Pulse was 68, blood pressure 120 mm. Hg systolic and 70 mm. diastolic. Laboratory examinations showed a normal leukocyte count, sedimentation rate, and urine. The temperature was 99° F. on admission and remained normal during his stay in the hospital. Roentgen-ray examination of the chest on admission showed a small left apical pneumothorax. Three days later roentgen-ray examination again showed the pneumothorax and a small linear area of emphysema along the left heart border. After 18 days the pneumothorax and emphysema were completely reabsorbed. He quickly obtained relief with 0.030 gm. of codeine sulfate and bed rest and had no more discomfort. The precordial sounds were audible in diminishing intensity for seven days. He was kept at bed rest for three weeks and then allowed up for light activity. On the thirtieth hospital day while sitting in the barber's chair he suddenly had left chest pain which was again associated with pain and numbness in the left shoulder. On resting the pain became less, but on walking it quickly became much worse. About one hour after the onset of the pain he noticed the crackling sensations over his heart. Examination showed the same findings as on admission. The precordial sounds were audible for four days and then disappeared. Roentgen-ray examination did not show a pneumothorax but did show a linear area of emphysema along the left heart border. Electrocardiograms showed no abnormalities in the limb leads. In the precordial leads V₁ showed an in-

verted T-wave and V_2 a diphasic T-wave. V_5 was of low amplitude. Four days later the precordial curves showed all T-waves upright and of greater amplitude.

Comment. This is a classical example of spontaneous mediastinal emphysema with recurrence. It is interesting in the history of the recurrence that the pain in the chest appeared approximately one hour before the patient noted the sounds over the heart. This is the story one would expect with a rupture of an alveolus and dissection back along the vascular channels bringing on the original pain. With the arrival of the air in the mediastinum the heart signs then become evident.

Case 4. A 20 year old white male was admitted to the hospital on June 24, 1944, complaining of pain in the chest and shortness of breath. On the previous day while playing tennis he had suddenly experienced a severe pain in the left upper and right lower chest posteriorly, as he was raising his left arm in order to serve. The pain was aggravated by attempts at deep inspiration. At the same time, he felt "dizzy," as if he were going to faint. He had slight dyspnea and cough. He immediately stopped playing and went to bed. He fell asleep, despite the persistence of the pain, but was awakened by inability to "catch his breath." This was relieved only by sitting up in a "hunched-over" position. After half an hour of sitting in this position he was able to fall asleep again. The next day pain persisted and patient was aware of gurgling sounds in his left chest.

On examination, he was found to prefer lying on his left side. He appeared to be in no distress. A few fine râles were heard along the lower left border of the sternum and in the left posterior chest at the level of the ninth and tenth thoracic vertebrae. At the cardiac apex and synchronous with the heart beat was a characteristic "crunching murmur." Roentgen-ray examination of the chest revealed a left apical pneumothorax with about 15 per cent collapse of the lung. Leukocyte counts and urinalyses were normal.

At bed rest the patient's pain quickly subsided, although the crunching sounds continued to be heard for two weeks. The temperature remained normal. Two weeks after admission he had a recurrence of severe pain in the left anterior chest and in the epigastrium with an increase in the number of crackling sounds heard over the heart. For several days he continued to have a sense of tightness in his epigastrium, and then all discomfort and physical signs gradually disappeared. He was discharged to duty on August 2, six weeks after admission, roentgen-ray examination having shown complete resorption of air.

Comment. This is another typical instance of spontaneous mediastinal emphysema, although the patient was indulging in heavy physical exercise at the time of its onset. He apparently had a mild recurrence while at bed rest. The epigastric pain and discomfort suggested retroperitoneal extension of the air at the time of the recurrence.

Case 5. A 21 year old white male was admitted to the hospital on August 15, 1944 complaining of pain in the left chest and shortness of breath. On the previous day while walking along the street he was suddenly seized with a sharp pain in the lower left chest, with radiation to the precordium and the left shoulder. He was unable to take a deep breath without intensifying the pain. His symptoms persisted until the morning of admission. At this time he was able to take a deep breath only when in a sitting position.

Physical examination showed the patient to be in no acute distress. The amplitude of excursions of the left thorax was diminished. Breath sounds and vocal and

tactile fremitus were also diminished on this side. A few "crackling" sounds were heard in an area one to two inches to the left of the mid-sternum. Roentgenographic examination of the chest showed a left pneumothorax with 60 per cent compression of the upper lobe and 30 per cent compression of the lower lobe. There was a moderate mediastinal herniation to the right. Leukocyte counts were normal.

Two days after admission "gurgling and crackling" sounds were heard over the heart, and in addition numerous metallic tapping sounds of a different character were noted in the same area. The patient's pain subsided almost immediately with the institution of rest and the adventitious sounds of both types gradually diminished until September 11, about four weeks after admission, the roentgen-ray examination was negative, and no further abnormal sounds were heard. The remainder of the hospital stay was uneventful and the patient was discharged to duty on October 30.

Comment. The pneumothorax in this case was of greater extent than in the previous cases, and it was possible to distinguish two entirely distinct types of adventitious sounds over the heart. One was the crunching or bubbling type as heard in the previous cases, whereas the second was of the metallic knocking type, which Greene has pointed out is associated with a left pneumothorax occasionally.

Case 6. A 23 year old white male soldier was admitted to the hospital on September 6, 1944, with a history of recurrent attacks of left anterior chest pain since December 1943. The pain first made its appearance while the patient was running and lasted for several hours. Since that time the pain had recurred about five times a month and usually lasted about half a day each time, although on one occasion it persisted for two days. Physical training and running were the most frequent precipitating factors. The patient also had considerable belching and attributed his symptoms to "gas." He was an aviation cadet, and when he started flying the attacks increased in frequency, although they did not necessarily come on while he was flying. He also began to have headaches with the attacks. Both belching and headaches were aggravated directly while he was flying. He was hospitalized at another hospital in July 1944 and was told that he had a heart murmur, but that the pain in the chest was due to a "strained muscle." He was eliminated from cadet training and was grounded.

The frequency of attacks became less after he was grounded, but he still had them in a fairly mild degree several times a month.

One hour before the present admission while standing in a line at the mess he experienced the most severe pain of all. It was sudden, was felt in the anterior aspect of the left chest, and made him want to "double up." No cough or shortness of breath accompanied the pain, but he did have a sense of palpitation.

Examination showed him to be irritable and depressed, but only moderately uncomfortable from the pain. Excursions of the left chest were limited, and there were diminished heart sounds and hyperresonance on this side. Blood pressure was 136 mm. Hg systolic and 80 mm. diastolic. On the day of admission, no adventitious sounds were heard over the heart and the diagnosis of left spontaneous pneumothorax was made. On the following day, however, numerous crunching and crackling sounds were heard over the heart. On the next day, they again were not elicited, but from then on sounds described as "tissue paper crackling" were heard for two weeks.

Roentgen-ray examination of the chest on the day after admission showed a left pneumothorax with an upper lobe collapse of about 50 per cent and a lower lobe collapse of about 25 per cent. There was moderate thickening of the visceral pleura over the upper lobe with a small adhesion over the apex. There was no mediastinal shift.

Three days later the roentgen-ray examination showed considerable reëxpansion of the lung. The upper lobe was only 40 per cent compressed, and the lower lobe had almost completely reëxpanded. At this time there was a moderately dense line parallel to the left border of the heart and about 0.5 cm. distance from it. An area of increased radiolucency was present between this line and the cardiac border. This was best observed in the region of the cardiac waist.

Leukocyte counts and electrocardiograms were normal.

The patient's symptoms quickly subsided and after four weeks there were no abnormal physical or radiographic signs.

Comment. This case is of particular interest for several reasons. First, it illustrates the necessity of searching carefully for the signs of mediastinal emphysema in every case of pneumothorax. Both the initial physical and roentgenographic examinations elicited only signs of a pneumothorax. Second, although the long previous history of recurrent chest pain, headache, and belching is difficult to interpret precisely (functional symptoms cannot be excluded), the possibility is suggested that this is an instance of repeated attacks of mediastinal emphysema. The similarity to case 2 should be noted. These two cases suggest that in certain cases mediastinal emphysema may appear to run a chronic course different from the classical description of a sudden acute attack with quick complete recovery after bed rest. If this interpretation is accepted, the exacerbation of symptoms by flying would confirm the observations of Lovelace and Hinshaw.²⁴

Case 7. An 18 year old white male was admitted to the hospital October 8, 1945 complaining of pain in the right lower chest. The pain had appeared suddenly on October 7 without exertion and persisted until the time of admission. The pain was aggravated by breathing. There was no cough and no respiratory infection. Three weeks previously, after returning from a hike, he had experienced a similar attack of pain in the right chest. He rested in his quarters for a half day and had no more pain until the present attack. Family and past history were otherwise non-contributory.

Physical examination on admission showed a well nourished boy complaining of pain in the right chest. The lung fields were normal to auscultation and percussion. Over the mid sternum were heard clicking, crunching sounds systolic in time and varying with respiration.

Roentgen-ray examination on the third hospital day showed a small right apical pneumothorax. Hemoglobin, erythrocyte, leukocyte, and differential counts were normal. Urine examination was normal. Sputum culture showed only alpha streptococci. Sedimentation rates were normal throughout his hospital stay. Electrocardiograms were within normal limits. Temperature, pulse and respiratory rates were not abnormal.

The pain was relieved by bed rest. The typical sounds over the sternum were heard in diminishing intensity for one week. On the tenth hospital day roentgen-ray examination of the chest showed complete reëxpansion of the lung with no evidence of pulmonary disease. He was discharged to duty after 22 days in the hospital.

Comment. This case represents a typical acute mediastinal emphysema. It is probable from the history of a similar attack three weeks before that this episode was a recurrence. It is interesting that in this case we observed a right apical pneumothorax. It is unusual, for in most cases reported the small pneumothorax occurs over the left apex.

DISCUSSION

These seven cases illustrate some of the problems of diagnosis and prognosis in acute mediastinal emphysema. The one certain diagnostic sign is the occurrence of crunching, crackling, popping sounds over the heart. Once heard they can be confused with no other cardiac sounds. The development of subcutaneous emphysema of the neck confirms the diagnosis. Every patient with a spontaneous pneumothorax, especially if it is small, should be carefully examined for the presence of mediastinal emphysema. One of our patients was thought to have only a spontaneous pneumothorax until re-examination the day after admission revealed the typical sounds over the precordium. Once one is familiar with the syndrome it should not be difficult to differentiate it from other diseases. The two diseases most commonly confused are acute pericarditis and coronary occlusion with myocardial infarction. Careful auscultation of the heart will establish the correct diagnosis.

The dangers of recurrence in this condition have not been stressed in previous reports. Apparently it is an important problem. One of our cases had a recurrence four weeks after his original attack. Two others had either recurrent attacks or a slow leak of air which gave almost constant symptoms for six to nine months. A fourth had a recurrence while at bed rest. A fifth had a previous episode from the history.

We feel the treatment should consist of prolonged bed rest until healing of the rupture is assured. We also administered sulfadiazine in moderate dosage for several days as a prophylactic against mediastinitis. This complication has not been reported, but it seems a possibility with a connection between the respiratory tract and the mediastinum especially if there is an associated respiratory infection.

SUMMARY

1. Seven cases of mediastinal emphysema are presented. One was associated with an acute respiratory infection and bronchial asthma, and six were spontaneous.

2. Five cases experienced a recurrence of this condition, and in two of these there were prolonged symptoms over six to nine months.

3. All six spontaneous cases had an associated pneumothorax. The necessity for careful examination of the precordium for mediastinal emphysema in cases with a small left apical pneumothorax is emphasized.

4. The clinical picture and problems of diagnosis and treatment are discussed.

BIBLIOGRAPHY

1. HAMMAN, L.: Spontaneous interstitial emphysema of the lungs, *Trans. Assoc. Am. Phys.*, 1937, lii, 311.
2. HAMMAN, L.: Spontaneous mediastinal emphysema, *Bull. Johns Hopkins Hosp.*, 1939, lxiv, 1.

3. SCOTT, A. M.: Significance of anginal syndrome in acute spontaneous pneumomediastinum, *Lancet*, 1937, i, 1327.
4. MOREY, J. B., and SOSMAN, M. E.: Spontaneous mediastinal emphysema, *Radiology*, 1939, xxxii, 19.
5. MCGUIRE, J., and BEAN, W. B.: Spontaneous interstitial emphysema of the lungs, *Am. Jr. Med. Sci.*, 1939, cxcvii, 502.
6. WOLFF, B. P.: Spontaneous mediastinal emphysema, *Ann. Int. Med.*, 1940, xiii, 1250.
7. CALDWELL, H. W.: Spontaneous mediastinal emphysema, *Jr. Am. Med. Assoc.*, 1941, cxvi, 301.
8. MATTHEWS, E.: Spontaneous mediastinal emphysema, *New Orleans Med. and Surg. Jr.*, 1941, xciii, 523. Cited by McGuire and Bean.⁵
9. PINCKNEY, M. M.: Mediastinal emphysema and idiopathic spontaneous pneumothorax, *Virginia Med. Monthly*, 1941, lxviii, 315. Cited by McGuire and Bean.⁵
10. STYRON, C. W.: Spontaneous mediastinal emphysema, *New England Jr. Med.*, 1941, ccxxv, 908.
11. GRIFFIN, R. J.: A diagnostic sign of spontaneous interstitial emphysema of the mediastinum; case reports, *Ann. Int. Med.*, 1942, xvii, 295.
12. KELLOGG, D. S.: Spontaneous pneumomediastinum (mediastinal emphysema), *Am. Jr. Roentgenol.*, 1942, xlviii, 510.
13. GREENE, J. A.: Unusual sounds emanating from the chest; cause and diagnostic significance of bubbling, clicking, crunching, knocking, and tapping sounds; with a report of two cases of interstitial emphysema of the lung and mediastinum, *Arch. Int. Med.*, 1943, lxxi, 410.
14. MONROE, D. S., and WEBB, G. A. C.: Spontaneous mediastinal emphysema, *Canad. Med. Assoc. Jr.*, 1943, xlviii, 232.
15. LINTZ, R. M.: Spontaneous mediastinal emphysema, *Arch. Int. Med.*, 1943, lxxi, 256.
16. ADCOCK, J. D.: Spontaneous interstitial emphysema of the lung with mediastinal, retroperitoneal, and subcutaneous emphysema, *Arch. Int. Med.*, 1943, lxxi, 650.
17. HOFFMAN, A. M., POBIRS, F. W., and MERLISS, R.: The phonocardiogram in spontaneous interstitial emphysema of the mediastinum, *Am. Heart Jr.*, 1943, xxvi, 686.
18. COWART, J. T.: Mediastinal emphysema. Report of two cases, *U. S. Naval Med. Bull.*, 1944, xliii, 119.
19. REES, W. A., and HUGHES, G. S.: Wounds of the chest as seen at an advanced operating centre, *Lancet*, 1918, i, 55.
20. BUKLEY, J. K., and COFFIN, T. H.: Generalized interstitial emphysema and spontaneous pneumothorax as complications of bronchopneumonia, *Jr. Am. Med. Assoc.*, 1919, lxxii, 535.
21. TORREY, R. C., and GROSH, L. C.: Acute pulmonary emphysema observed during the epidemic of influenzal pneumonia at Camp Hancock, Georgia, *Am. Jr. Med. Sci.*, 1919, clvii, 170.
22. KELMAN, S. R.: Experimental emphysema, *Arch. Int. Med.*, 1919, xxiv, 332.
23. MONTO, R. W., and WOODALL, P. S.: Mediastinal emphysema resulting from exposure to a pulmonary irritant, *War Med.*, 1944, vi, 251.
24. LOVELACE, W. R., and HINSHAW, H. C.: Aerial transportation of patients. With special reference to traumatic pneumothorax, diaphragmatic hernia and mediastinal emphysema, *War Med.*, 1942, ii, 580.
25. JESSUP, P. M.: Mediastinal emphysema, *Arch. Surg.*, 1931, xxiii, 760.
26. NEFFSON, H. A.: Tension pneumothorax and mediastinal emphysema after tracheotomy. General study with analysis of seventeen cases in a series of 126 tracheotomies for acute obstructive infections of the larynx, trachea and bronchi during the past decade, *Arch. Otolaryngol.*, 1943, xxxvii, 23.
27. MARCOTTE, R. J., PHILLIPS, F. J., ADAMS, W. E., and LIVINGSTONE, H.: Differential intrabronchial pressures and mediastinal emphysema, *Jr. Thoracic Surg.*, 1940, ix, 346.

28. MATSUZAWA, D.: Mediastinal emphysema as a complication of artificial pneumothorax. Report of case, *Quart. Bull. Sea View Hosp.*, 1937, ii, 173. Cited by Smith and Bowser.⁴¹
29. BANYAI, A. L., and JURGENS, G. H.: Mediastinal emphysema as a complication of artificial pneumoperitoneum, *Jr. Thoracic Surg.*, 1939, viii, 329.
30. VINCENT, J.: Emphyseme generalise spontane au cours d'une bronchopneumonie sans atteinte pleurale, *Ann. d'anat. path.*, 1936, xiii, 377.
31. NEFFSON, A. H., and BULLOWA, J. G. M.: Influenza with simultaneous bilateral spontaneous pneumothorax and subcutaneous emphysema, *Arch. Otolaryngol.*, 1938, xxviii, 388.
32. FAULKNER, W. B., and WAGNER, R. J.: Fatal spontaneous pneumothorax and subcutaneous emphysema in an asthmatic, *Jr. Allergy*, 1936, viii, 267.
33. ELLIOTT, R. W.: Subcutaneous emphysema and pneumothorax in bronchial asthma, *Lancet*, 1938, i, 1104.
34. MEADE, R. H., and STAFFORD, F. B.: Spontaneous interstitial emphysema in pulmonary tuberculosis. Report of a case successfully treated by operation, *Am. Rev. Tuberc.*, 1930, xxi, 579.
35. STANLEY, R.: Interstitial emphysema during labour, *Brit. Med. Jr.*, 1943, i, 477.
36. BIERING, A.: Pneumothorax in the newborn. A case of pneumothorax with congenital atelectasis and mediastinal emphysema, and some remarks on the pathogenesis with special reference to the importance of congenital atelectasis, *Acta Paediat.*, 1941, xxviii, 367.
37. GUMBINER, B., and CUTLER, M. M.: Spontaneous pneumomediastinum in the newborn, *Jr. Am. Med. Assoc.*, 1941, cxvii, 2050.
38. MACKLIN, C. C.: Transport of air along sheaths of pulmonic blood vessels from alveoli to mediastinum. Clinical implications, *Arch. Int. Med.*, 1939, lxiv, 913.
39. JOANNIDES, M., and TSOULOS, G. D.: The etiology of interstitial and mediastinal emphysema, *Arch. Surg.*, 1930, xxi, 333.
40. DOLGOPOLOV, V. B., and STERN, M. E.: Interstitial emphysema of the lung with spontaneous pneumothorax and subcutaneous emphysema—demonstration of air in the septums of a human lung, *Arch. Otolaryng.*, 1940, xxxi, 140.
41. SMITH, A. B., and BOWSER, J. F.: Spontaneous pneumomediastinum (mediastinal emphysema) with reports of two cases in infants, *Radiology*, 1942, xxxviii, 314.
42. SMITH, S. M.: Pericardial knock, *Brit. Med. Jr.*, 1918, i, 78.
43. HAMMAN, L.: A note on the mechanism of spontaneous pneumothorax, *Ann. Int. Med.*, 1939, xiii, 923.
44. GAUDRAULT, G. L., and CHALMERS, D. M.: Emergency treatment of traumatic emphysema of the mediastinum, *New England Jr. Med.*, 1941, ccxxiv, 940.

STUDIES ON TWO SPORADIC CRETINOUS BROTHERS WITH GOITER, TOGETHER WITH SOME REMARKS ON THE RELATION OF HYPERPLASIA TO NEOPLASIA *

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Our interest in the pathology and pathological physiology of cretinous goiters was stimulated by the discovery and study of two cretinous brothers, both possessing goiters. The results of this study, plus additional observations on two other cretinous subjects with goiter, on patients treated with thiouracil and on experimental animals, have been the basis of speculation regarding the rôle of hyperplasia in the genesis of neoplasia. Since studies of the type made on the two cretinous brothers are instructive, the results are presented below in detail, together with brief clinical histories.

CASE REPORTS

Case 1. R. W., a 19 year old white boy, was admitted to the Massachusetts General Hospital on October 4, 1944. He complained of a mass which had been present in his neck for seven years. He had apparently been essentially well and normal until the age of 10, when his mother remarked about his failure to grow. When he was 12 years old his mother noticed a swelling in his neck. The goiter increased in size until it reached the dimensions of a lemon. He was given thyroid $\frac{1}{2}$ grain (0.032 gram) and later 1 grain (0.065 gram) daily. He grew rapidly between the ages of 13 and 15, the size of the thyroid mass meanwhile remaining stationary. At 17, thyroid medication was discontinued, and the goiter began to enlarge again, eventually reaching the proportions of a large orange on each side.

Pubic hair began to appear when the patient was 16. Voice changes were first noted one month prior to admission. He left school at the age of 16 when in the fifth grade, and has since worked at many jobs but never lasted long in any because he was slow in his work.

The patient was born in Leister, Massachusetts, and lived in New Jersey and Maine for short periods. Since the age of five he has lived in Worcester, Massachusetts. The diet was adequate and did not include excessive amounts of goitrogenic foods such as cabbage and soy beans. There was no family history of endocrine disease. There were three siblings: a normal male, age 14; a male, C. W., age 12, presented below; and a normal female, age 4.

On physical examination the patient appeared well-proportioned and muscular (figure 1). He was 64 inches (163 centimeters) tall and weighed 139 pounds (63 kilograms). The skin was dry, rough, and pale. The hair was not remarkable. The eyes were set wide apart, the bridge of the nose was flat and the nostrils wide and flaring. The voice was husky. The thyroid was symmetrically enlarged, measuring 15 by 8 centimeters, firm in consistency, and without bruit.

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From the Thyroid Clinic of the Massachusetts General Hospital, Boston, Massachusetts.

Laboratory findings are in part listed in table 1. The urine and blood counts were normal. The bone age, as determined from roentgen-ray examination of the hands, was 18 years and three months, of the iliac crest, 17 years. The mental age was 10 years six months. The various chemical studies on the blood, the excretion of follicle-stimulating hormone (F.S.H.) and of the 17-ketosteroids in the urine, the glucose-tolerance test, the insulin-tolerance test, the Keppler water-diuresis test and the basal metabolism level of minus 28 were all consistent with his myxedematous state. The blood cholesterol, surprisingly enough, was normal—169 mg. per cent. There was no detectable amount of thiocyanate in the blood. When a tracer dose of radioactive iodine was administered to the patient, the goiter retained 87 per cent, indicating that the goiter had a strong avidity for iodine. The iodine content of the gland, as determined on a biopsy specimen, was low, namely 0.07 per cent.



FIG. 1. Antero-posterior and lateral view of two cretinous brothers, R. W. on the left and C. W. on the right of each view.

Histological examination of the biopsy specimen revealed a highly vascular tissue with loose arrangement in follicles and cords of varying size, mostly small, and a small amount of interstitial connective tissue (figure 2). The epithelium was high cuboidal to columnar and there was a small amount of colloid. Mitoses were not observed. The diagnosis was struma nodosa micro and macro folliculare.

Case 2. C. W., a 12-year old schoolboy, was admitted to the Massachusetts General Hospital at the same time as his brother R. W. At the age of five, he was found to have a goiter, at the same time it was discovered in his brother, and he, too, was placed on thyroid, $\frac{1}{2}$ grain (0.032 gram) at first and later 1 grain (0.065 gram) daily. Thyroid was discontinued in January 1943 when the basal metabolism was found to be plus 9. During the period of thyroid medication the goiter did not enlarge further but body growth was very slow. After thyroid was discontinued, the mass in the

TABLE I

Laboratory and Other Data on Two Cretinous Brothers with Goiter

	Case 1 (R.W.)	Case 2 (C.W.)
Age	19 years	12 years
Bone age (hands)	18 $\frac{3}{4}$ years	5 $\frac{3}{4}$ years
Mental age	10 $\frac{1}{2}$ years	8 $\frac{1}{2}$ years
Electrocardiogram	normal	normal
Chest roentgenogram	normal	normal
Blood cholesterol	169 mg. %	183 mg. %
Blood calcium	9.3 mg. %	9.0 mg. %
Blood phosphorus	2.5 mg. %	4.9 mg. %
Blood alkaline phosphatase	2.4 units	3.7 units
Blood sodium	137.5 m.eq./L.	138.8 m.eq./L.
Blood chloride	101.0 m.eq./L.	101.4 m.eq./L.
Serum protein	7.1%	6.7%
Glucose tolerance	<i>Blood Sugar</i>	<i>Blood Sugar</i>
Fasting	74 mg. %	80 mg. %
$\frac{1}{2}$ hour	98	111
1 hour	118	114
2 hours	87	114
3 hours	95	103
4 hours	89	89
5 hours	98	95
Insulin tolerance		
Fasting	100 mg. %	93 mg. %
20 minutes	67	65
30 minutes	75	63
45 minutes	80	68
60 minutes	75	—
90 minutes	82	63
120 minutes	87	61
(epinephrine 0.5 c.c. s.c.)		
45 minutes	100	103
60 minutes	118	95
F.S.H. excretion	pos. 6.5 m.u./24 hrs.	pos. 3 m.u./24 hrs.
17-ketosteroid	3.6 mg./24 hrs.	0.9 mg./24 hrs.
Keppler water-diuresis test	negative	negative
B.M.R. level	minus 28	minus 20
Collection of radio-iodine by gland	87%	58%
I ₂ content of gland	0.07%	—

neck increased in size, the skin became rough and the abdomen gradually became distended. He gained 10 pounds in the year preceding admission but did not increase in height. He walked slowly, seldom played games and was intolerant of the cold. He was slightly retarded mentally, being in the fifth grade at the time of admission. As in the case of his brother he had lived in Worcester, Massachusetts all his life and his diet was not excessive in any known goitrogenic foods.

On physical examination the patient appeared small and underdeveloped, with cretinoid facies (figure 1). He was 48 inches tall and weighed 54 pounds. The skin was warm, pale, and hyperkeratotic, especially over the abdomen. The thyroid was diffusely and moderately enlarged, consisting of soft, nodular tissue, more in the right lobe than in the left lobe; a bruit was not audible. The tongue was smooth and the voice hoarse and rather deep. The abdomen was protuberant and contained many fecal impactions.

The important laboratory findings in this case are also summarized in table 1. He had a slight anemia of 3.09 million red cells and 12 grams of hemoglobin. The urine was normal. The bone age was five years nine months, as determined by roentgen-ray examination of the hands; five years by examination of the femoral heads. The mental age was eight years and two months. As in Case 1, the various chemical determinations on the blood, the excretion of follicle-stimulating hormone

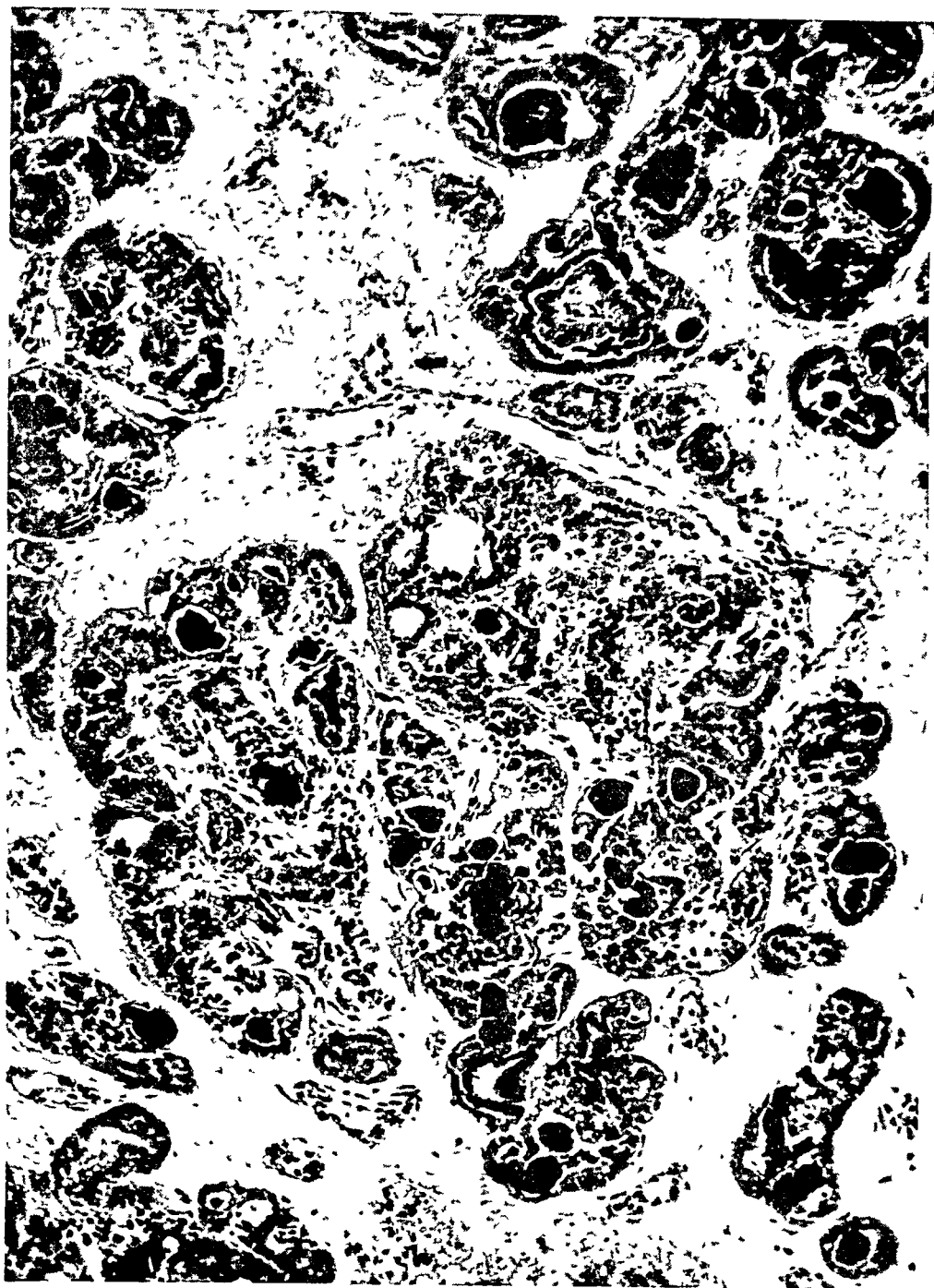


FIG. 2a. Low power view of a section of thyroid tissue from Case 1 (R. W.).

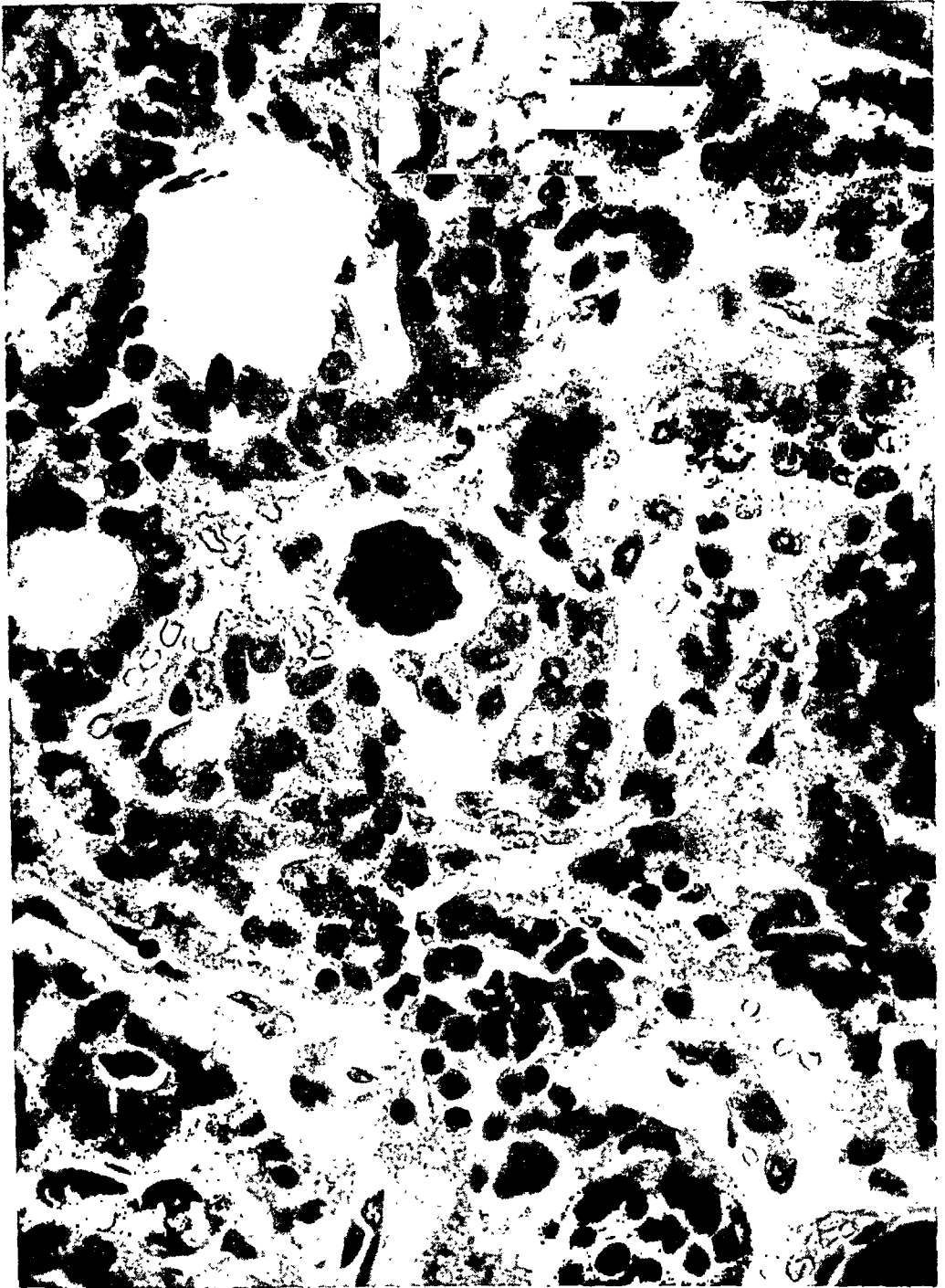


FIG. 2b. High power view of a section of thyroid tissue from Case 1 (R. W.).

(F.S.H.) and of the 17-ketosteroids in the urine, the glucose-tolerance test, the insulin-tolerance test and the Keppler water-diuresis test were all consistent with his cretinoid state. Again there was no detectable amount of thiocyanate in the blood. The metabolism varied considerably, reaching levels as low as minus 24, but averaged minus 20. The collection by the thyroid of a tracer dose of radioactive iodine amounted to 58 per cent.

Examination of a biopsy specimen of the thyroid disclosed a loose arrangement of glandular tissue in columns and clusters of cuboidal cells. The tissue was highly vascular and there was no colloid present (figure 3). The diagnosis was fetal adenoma.

The diagnosis of cretinism in these two cases seems to be well established. Their general appearance is strongly suggestive. The low metabolism, the retarded bone age, the retarded mentality and the various chemical and biological tests are all confirmatory. The normal blood cholesterol is a little disturbing. The low values for the excretion of follicle-stimulating hormone (F.S.H.) and of the 17-ketosteroids in the urine in Case 2, although consistent with cretinism, favors the diagnosis of hypopituitarism. However, the character of the insulin-tolerance test and the negative Keppler water-diuresis test argue for thyroid deficiency.

After a short period of iodine medication, both glands were removed. The histological sections revealed two interesting findings: (1) the pathological changes in the two specimens were similar; (2) the changes were not uniform. There were areas in each gland characteristic of fetal adenoma; other areas were typical of papillary cyst adenoma, of struma nodosa macro and micro folliculare and of colloid goiter (see figures 4 and 5).

DISCUSSION

In an endemic goiter area, a cretin with goiter is common; in a non-goiterous area, a cretin with goiter is rather rare. When present it must represent the result of the effort made by the gland to produce more hormone. The biological studies in these two cases, which indicate a low iodine content of the goiter (0.07 per cent) and a strong avidity for iodine, are consistent with an iodine-deficiency goiter. These findings agree with those of Hamilton, Soley, and Reilly¹ who found that the glands of eight cretin patients with atrophic thyroids took up less radioactive iodine than normal, whereas two goiterous thyroids took up excessive amounts. It is hard to visualize how iodine-deficiency can develop in this region. However, the ingestion of a positive goitrogen may also account for this type of goiter. In fact, low iodine-content and high iodine-uptake are found in sulfocyanate and cabbage goiters as well as in iodine-deficiency goiters (see Rawson, Tannheimer and Peacock²). As far as it could be determined, the diet of these two boys was apparently adequate in iodine and not excessive in cabbage, soy beans or related vegetables. To be sure, an unknown goitrogen cannot be ruled out. In any case, the gland, under these circumstances, should show hyperplasia. The actual changes in the gland were those which Marine and Lenhart³ associated with the process of hyperplasia. Some areas showed regression to colloid goiter; other areas consisted of solid cords of young cells, without tendency to follicle formation and with very little supporting structure, and of structures characteristic of papillary cyst ade-

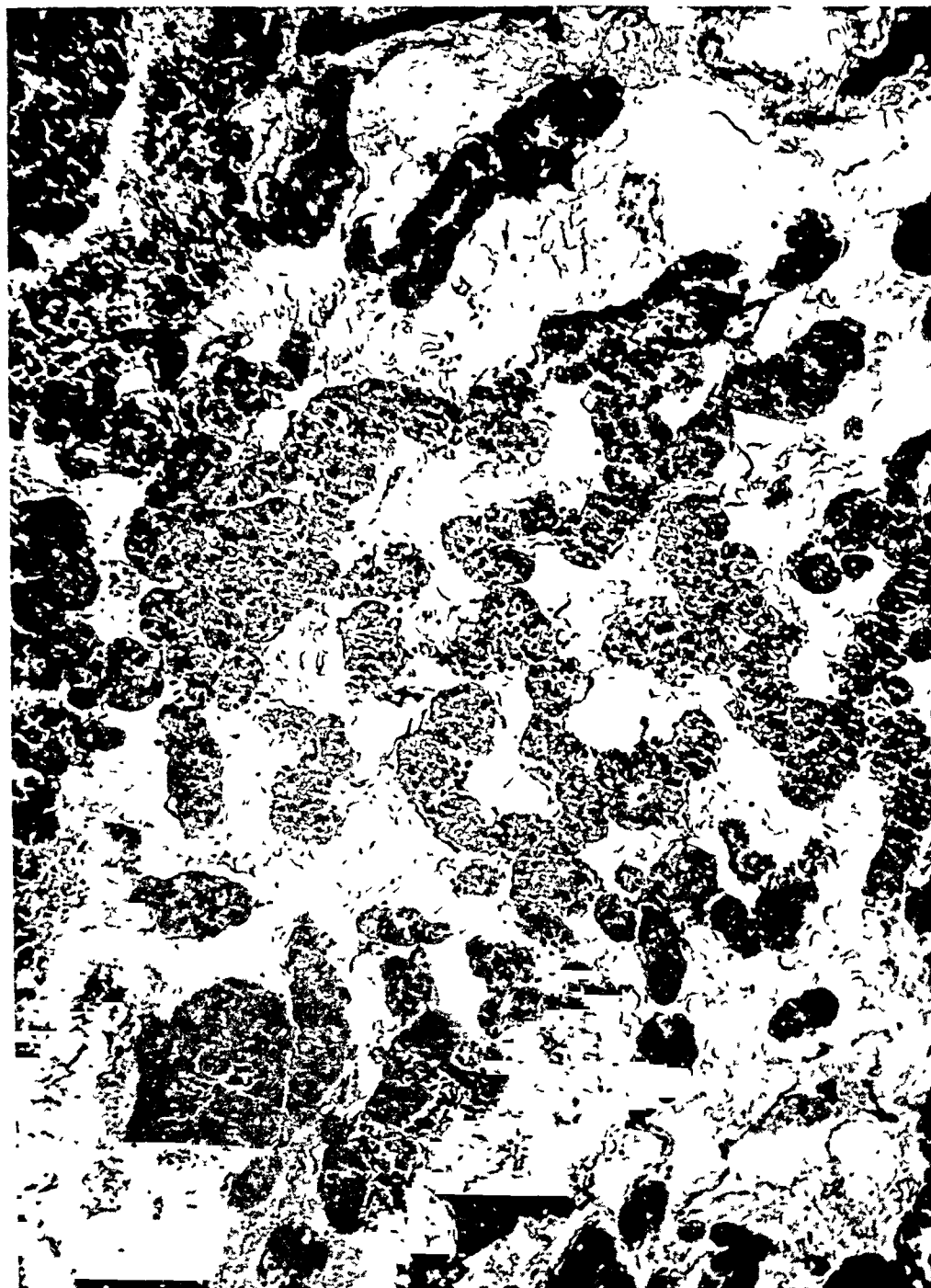


FIG. 3a. Low power view of a section of thyroid tissue from Case 2 (C. W.).

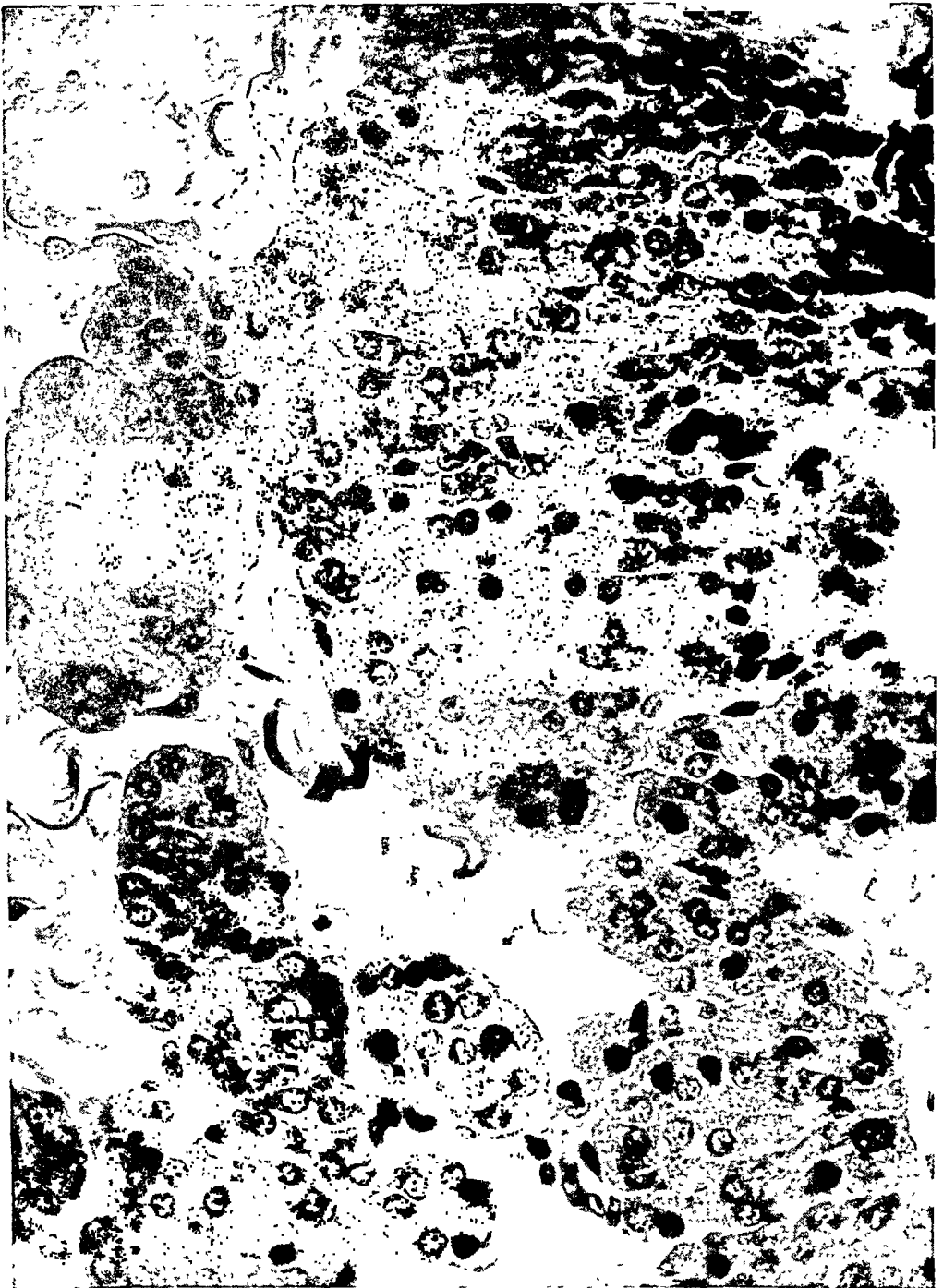


FIG. 3b. High power view of a section of thyroid tissue from Case 2 (C. W.).
Note the solid cords of tissue with very little supportive structure.

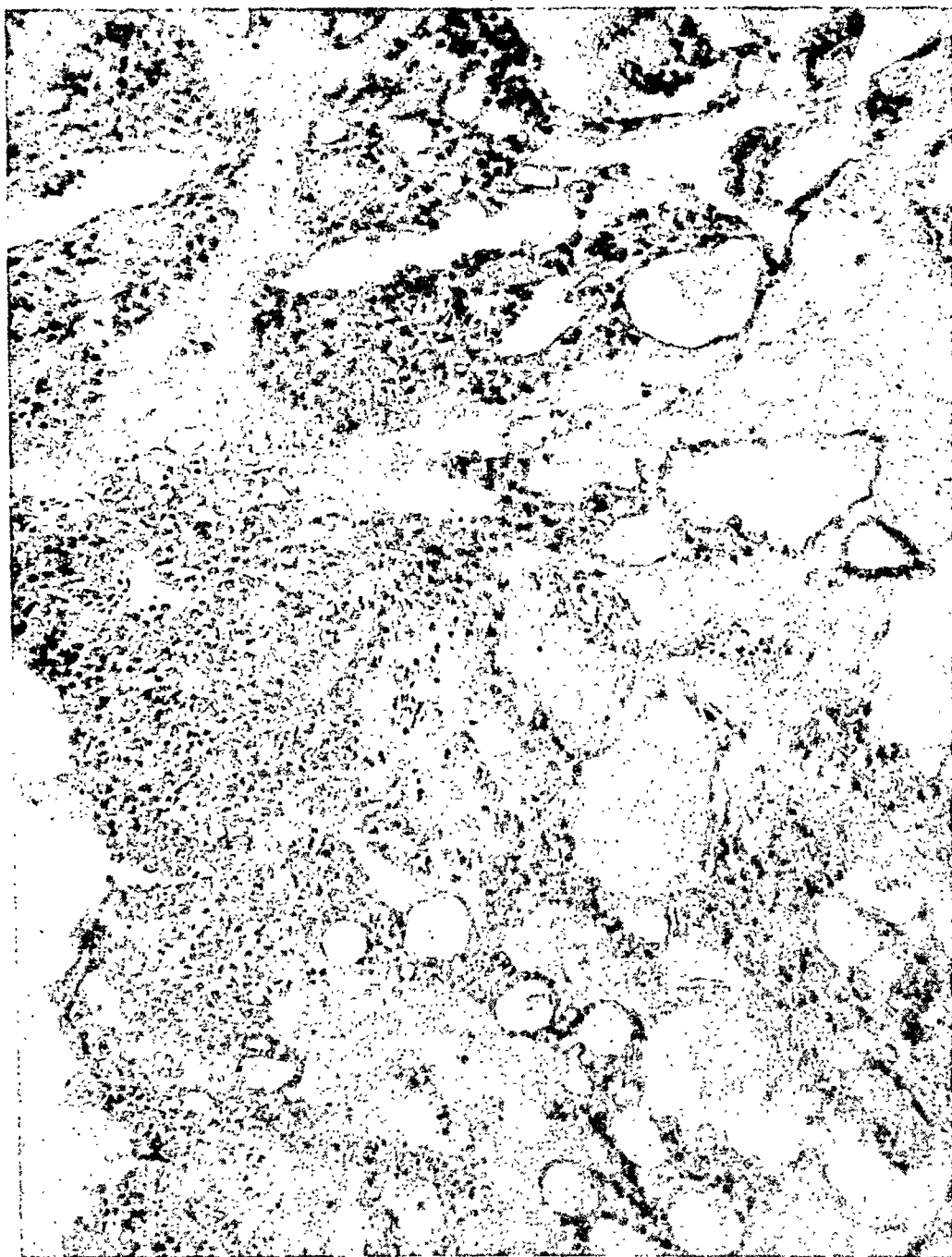


FIG. 4a.



FIG 4b.

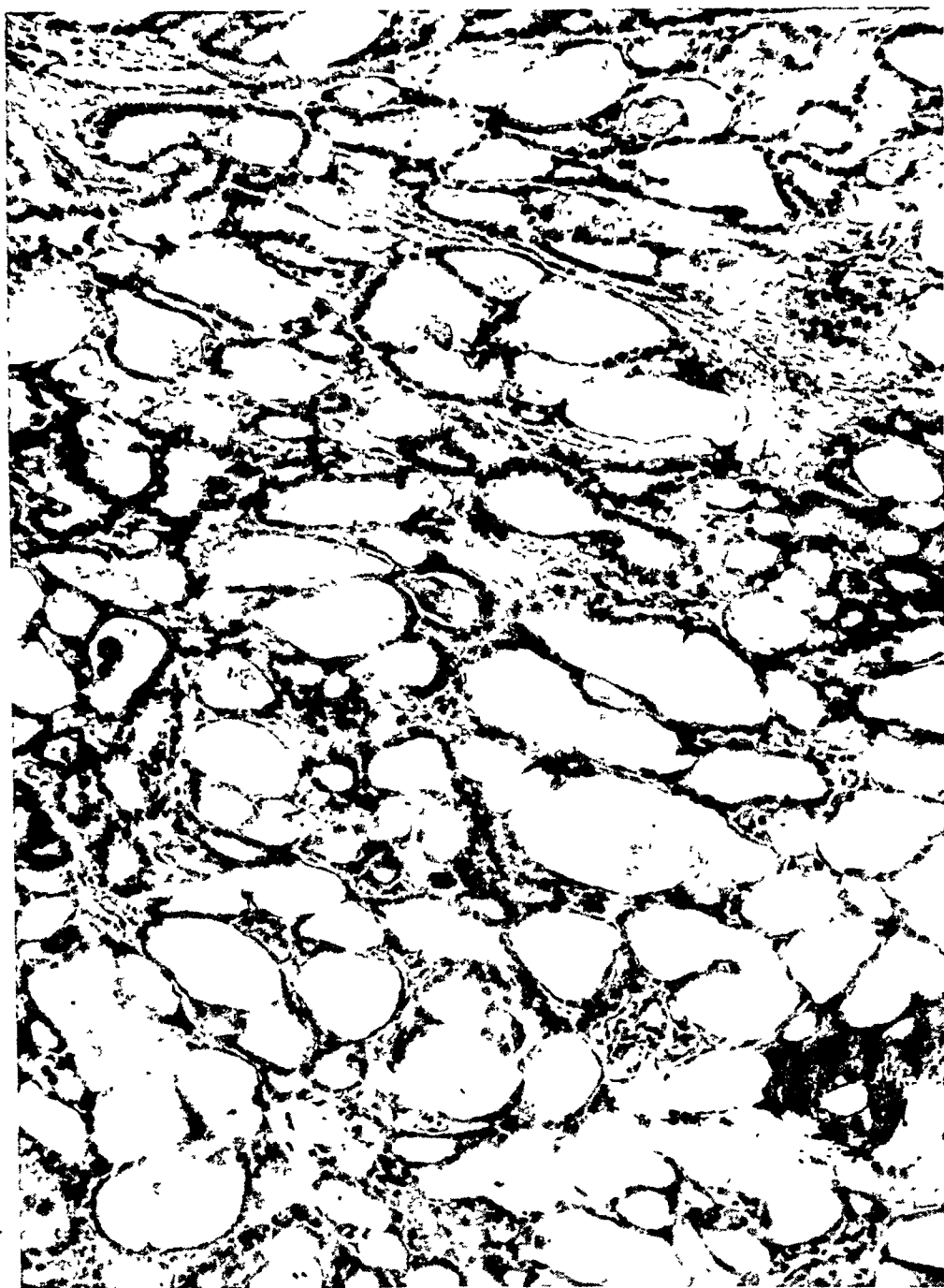


FIG. 4c.

FIG. 4. Three low power views of thyroid removed at operation in Case 1 (R. W.): (a) fetal adenoma; (b) papillary cyst adenoma; (c) colloid goiter tissue.

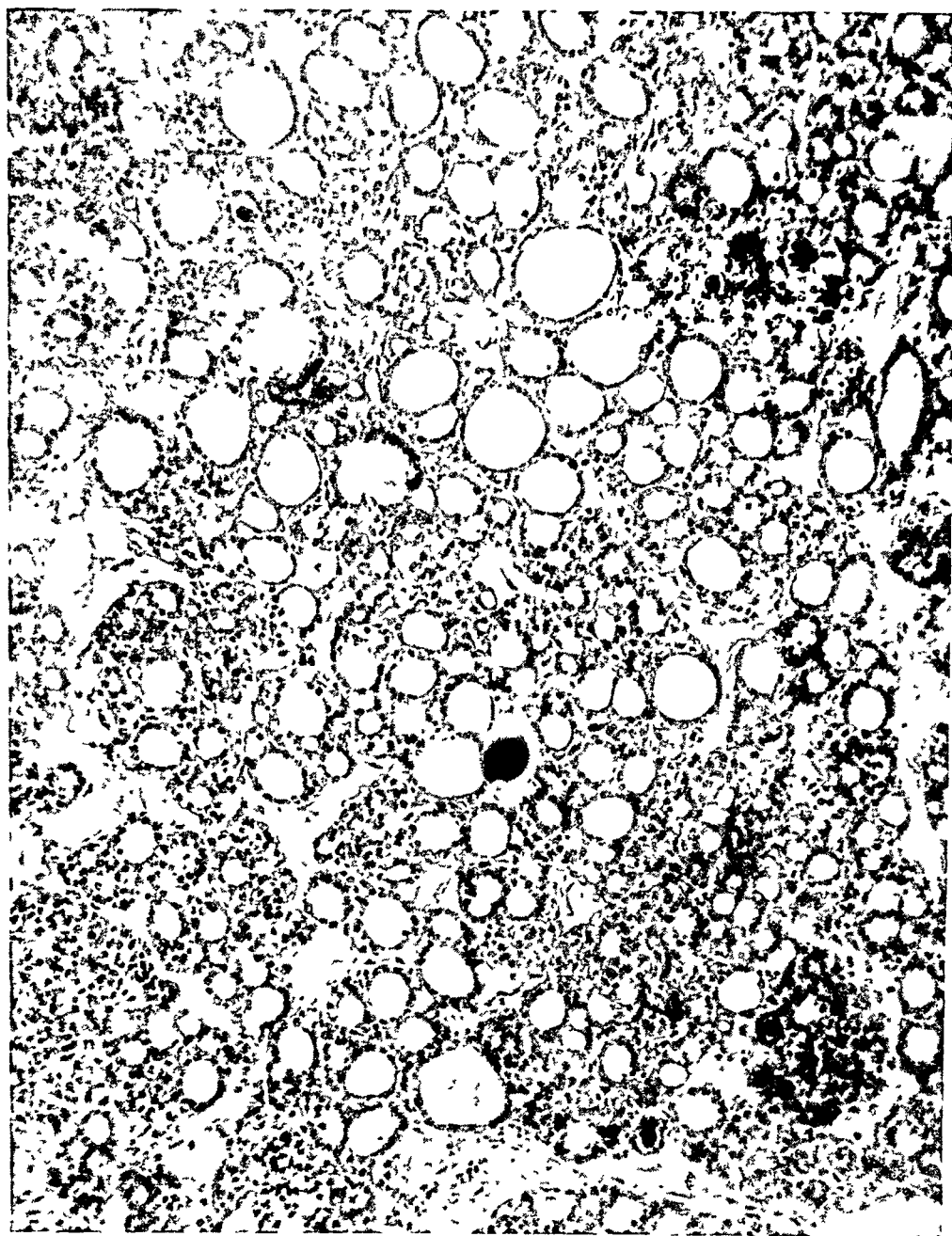


FIG. 5a.



FIG. 5b.

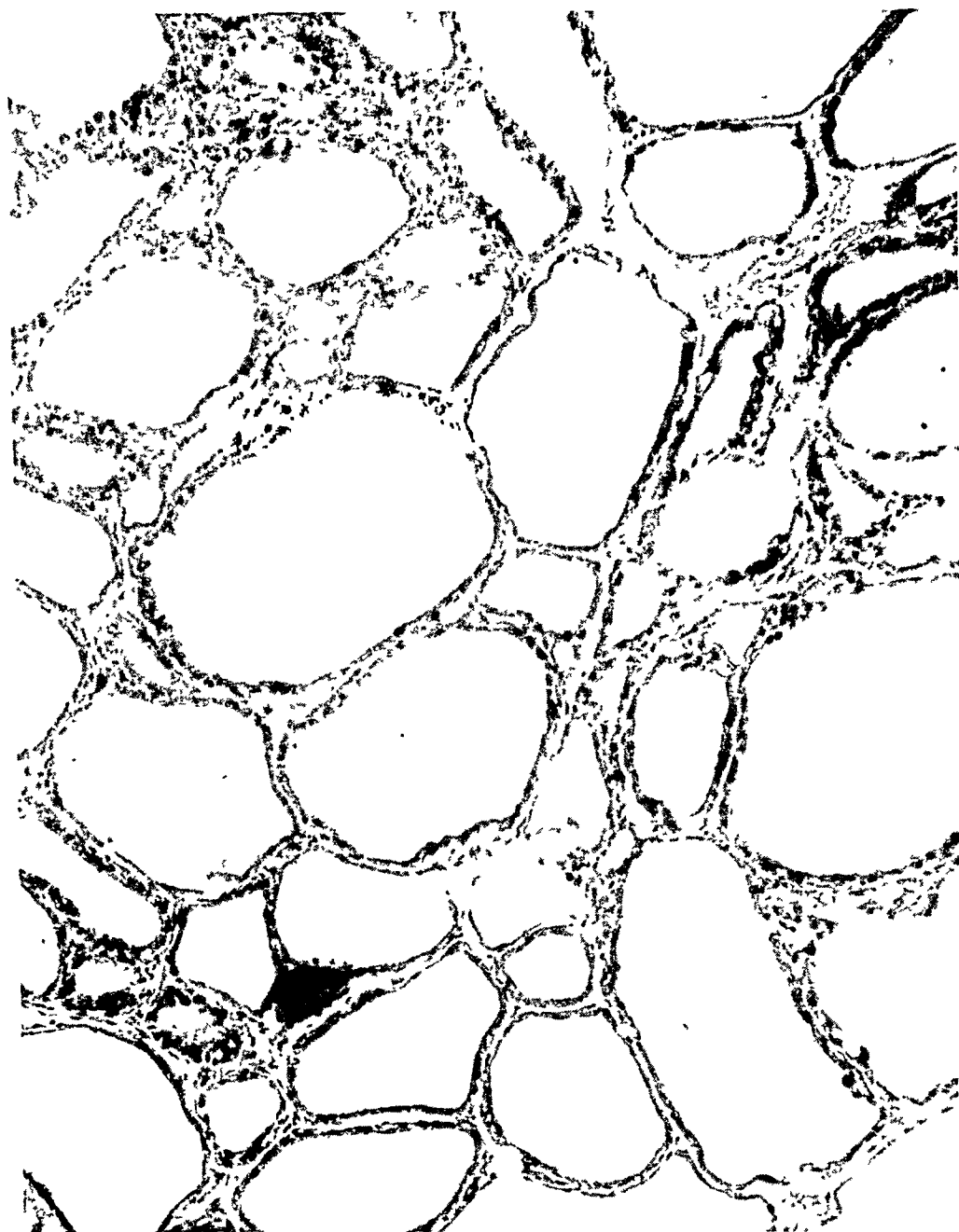


FIG. 5c.

FIG. 5. Three low power views of thyroid removed at operation in Case 2 (C. W.): (a) Struma nodosa macro and micro folliculare; (b) papillary cyst adenoma; (c) colloid goiter tissue.

noma. Both types are quite suggestive of pre-neoplastic or neoplastic changes.

These unusual findings led us to reexamine the records of two other cretins with goiter seen in 1942. One was a 13 year old boy (H. E.) living on the seacoast of Massachusetts, and was one of seven siblings, four of whom were cretins, two with and two without goiters. He had received thyroid and iodine for many years, but finally the gland, weighing 240 grams, was removed. The gland was extremely vascular and microscopically resembled the gland of C. W. (see figure 6). The other was a 21 year old girl (D. B.) who had a subtotal thyroidectomy for a nodular goiter weighing 160 grams. The tissue contained very little iodine, namely 0.01 per cent, and its microscopic structure simulated that of the gland from R. W. (see figure 7).

Two other bits of information are pertinent here. Recently we had the opportunity to examine sections of pigs' thyroids sent to Dr. R. W. Rawson by Dr. F. N. Andrews of Purdue University. These thyroids were removed from the offspring of pigs which had been fed a soy bean diet. These offspring were cretinous and had goiters which contained very little iodine (0.006–0.01 per cent). Some of these thyroids showed extensive hyperplasia (figure 8); others showed a structure not unlike struma nodosa macro and micro folliculare; and still others showed the solid structure of fetal adenoma (figure 9).

In ordinary Graves' disease, when thiouracil is administered for two or more weeks, the gland at operation shows a high degree of hyperplasia. In some cases in which thiouracil is administered for six weeks or longer before operation, the gland shows areas resembling the structure of fetal adenoma as well as areas of hyperplasia. In one instance in which thiouracil was administered for 10 months, the entire gland showed a microscopic appearance characteristic of struma nodosa macro and micro folliculare (figure 10).

These findings raise anew several questions regarding the relationship between hyperplasia and neoplasia. Is neoplasia the end-result of severe and extensive hyperplasia? What is the significance of apparently neoplastic changes in a gland which is clinically benign? Finally, what is the rôle in the pathogenesis of malignancy of agents which increase hyperplasia? A smattering of experimental and clinical data is available. Hellwig⁴ placed six white rats on a high calcium, low iodine diet. Hyperplasia occurred in all and in two, definite adenomata of the lobular, small follicle type. He believes that adenomata arise as a local hyperplasia of the epithelium, and that they represent an intermediate stage between hyperplasia and malignancy. The recent experimental observations by Bielschowsky⁵ are most illuminating. He observed that 2-acetyl-amino fluorine, when fed alone, caused malignant tumors of various organs in rats but never in the thyroid, whereas allyl-thiourea resulted in hyperplasia of the thyroid, but never neoplasia.

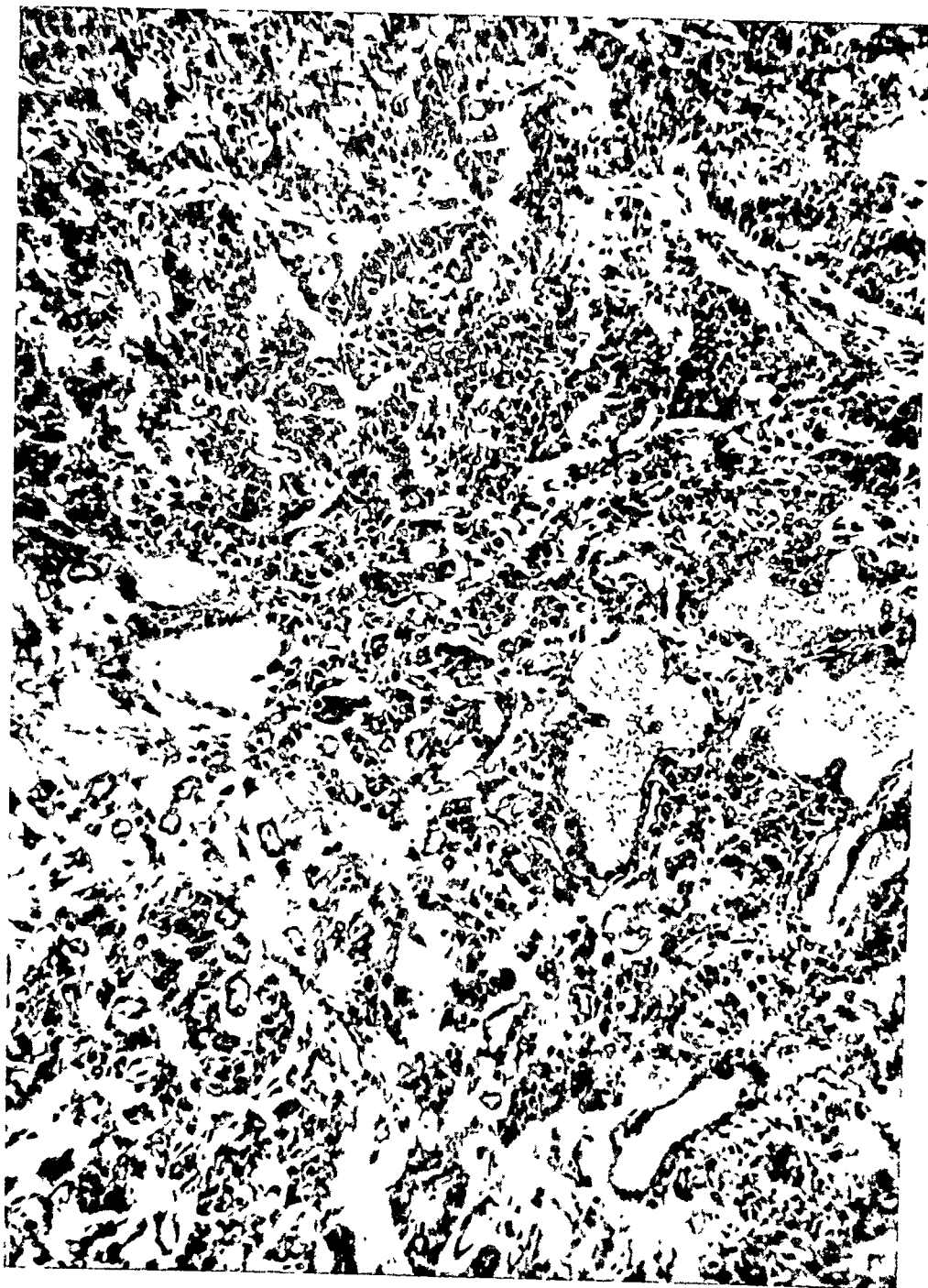


FIG. 6a. Low power view of a section of thyroid tissue from patient H. E.

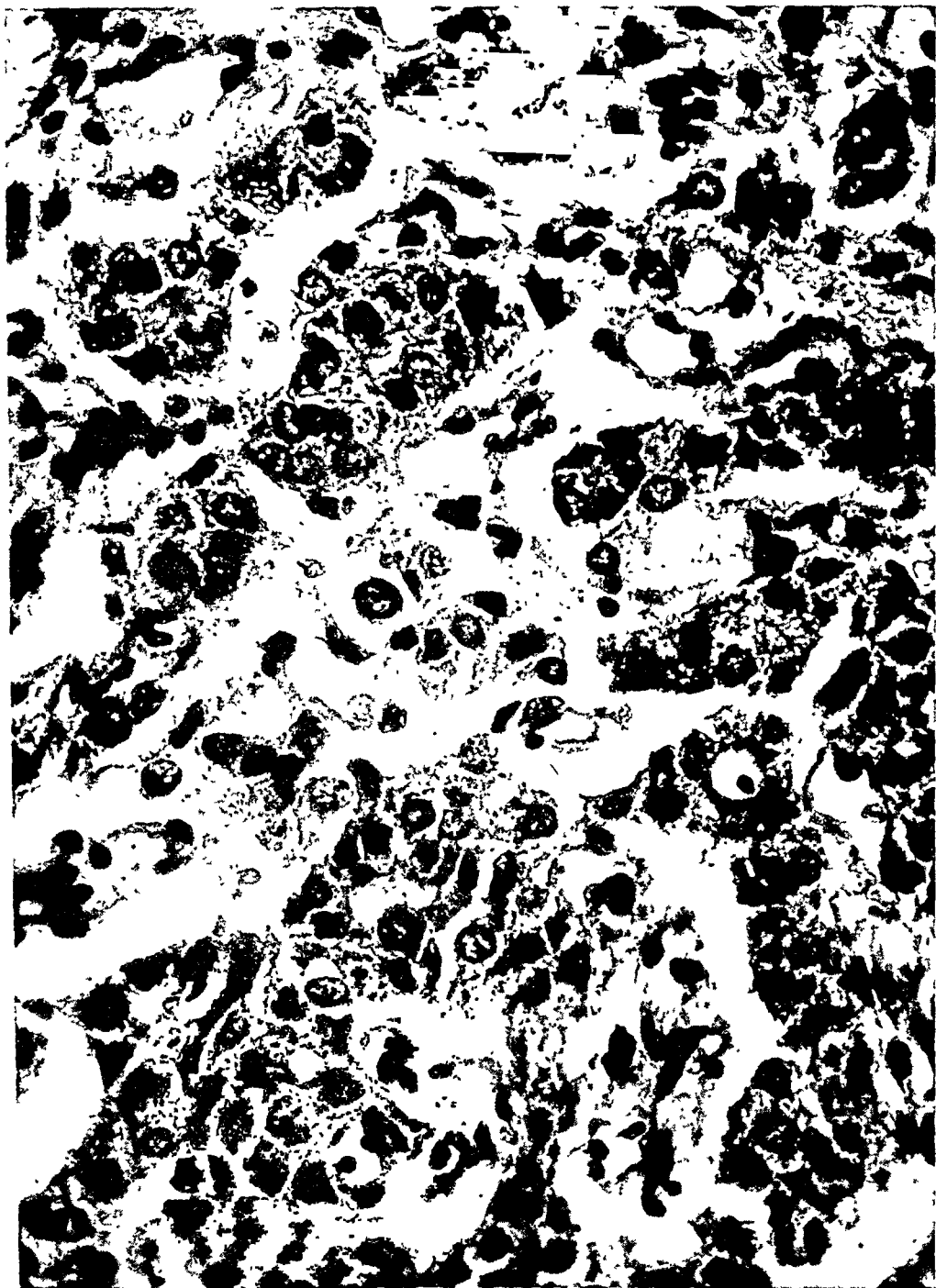


FIG. 6b. High power view of a section of thyroid tissue from patient H. E.



FIG. 7a. Low power view of a section of thyroid tissue from patient D. B.

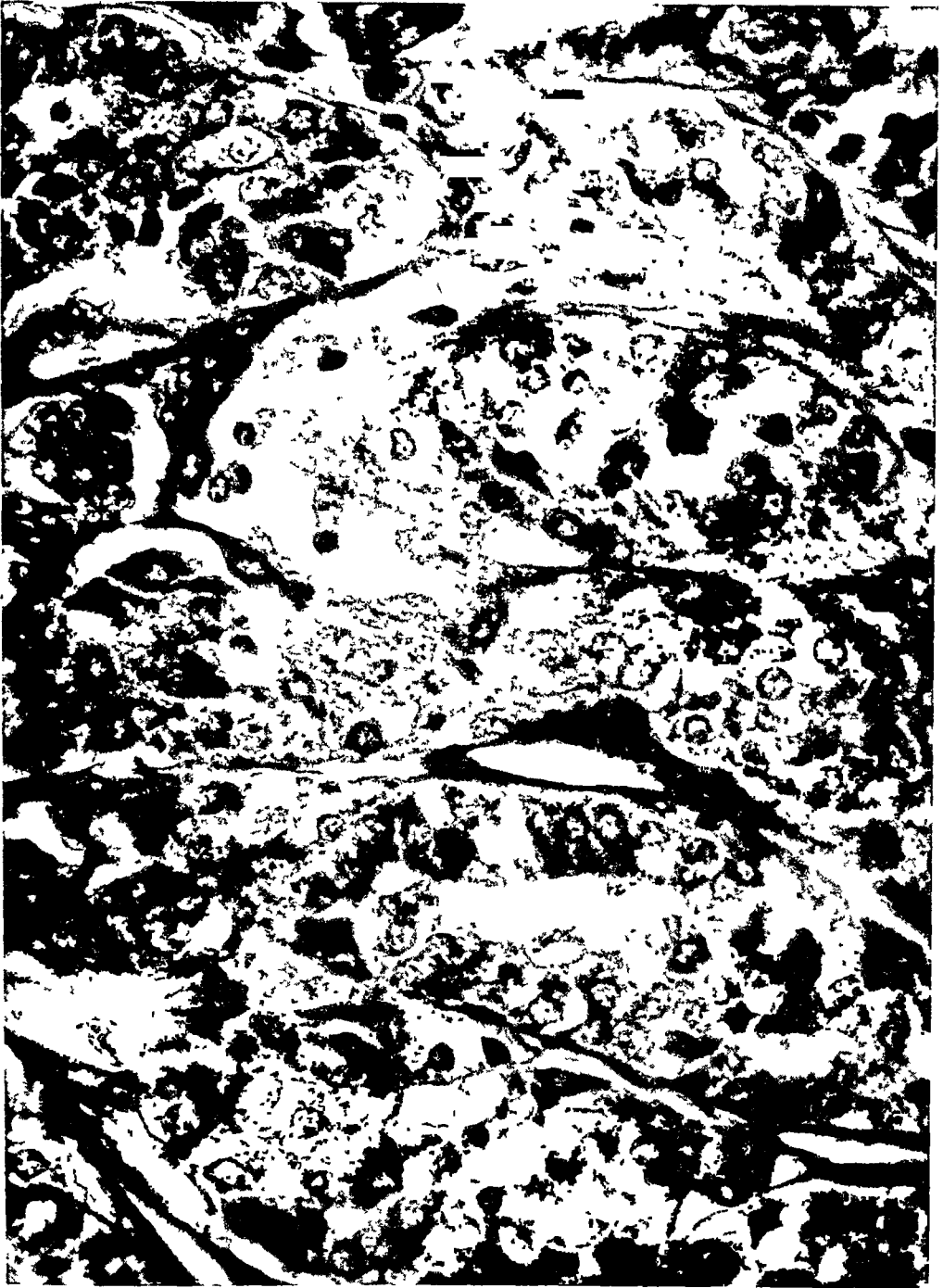


FIG. 7b. High power view of a section of thyroid tissue from patient D. B.

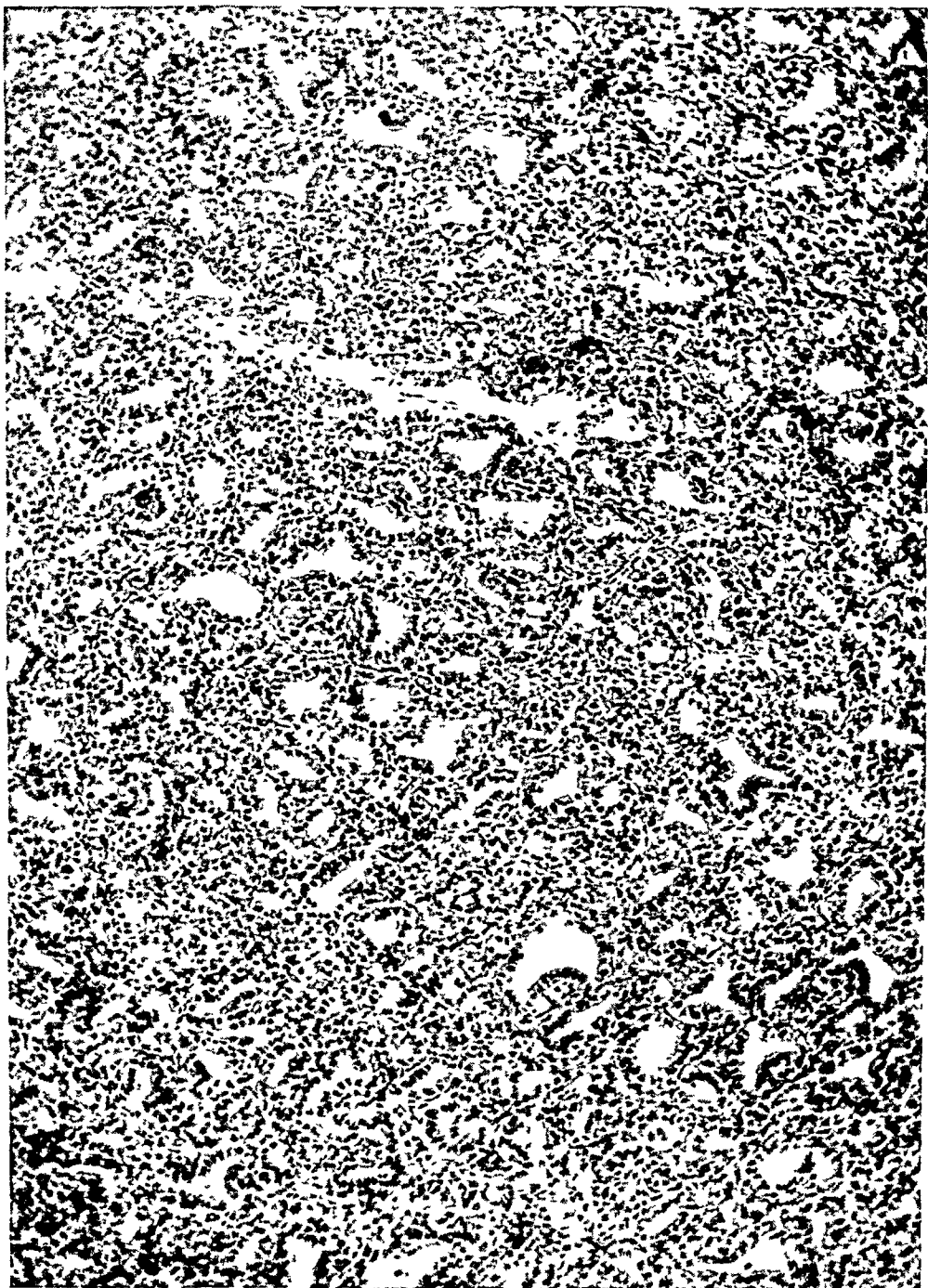


FIG. 8a. Low power view of a section of thyroid tissue from a cretinous pig, whose parents were on a soy bean diet.

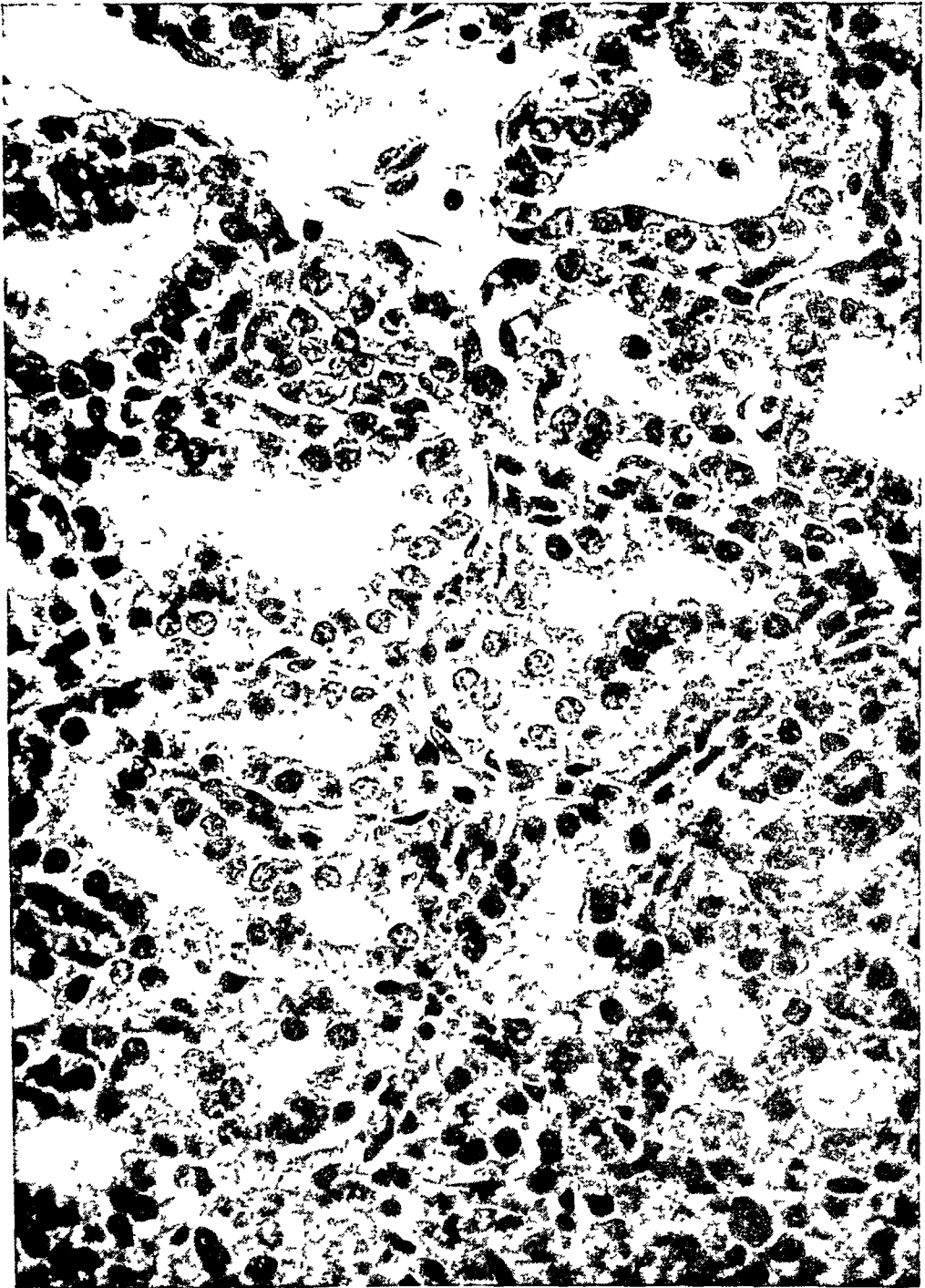


FIG. 8b. High power view of a section of thyroid tissue from a cretinous pig, whose parents were on a soy bean diet. Note the extensive hyperplasia.

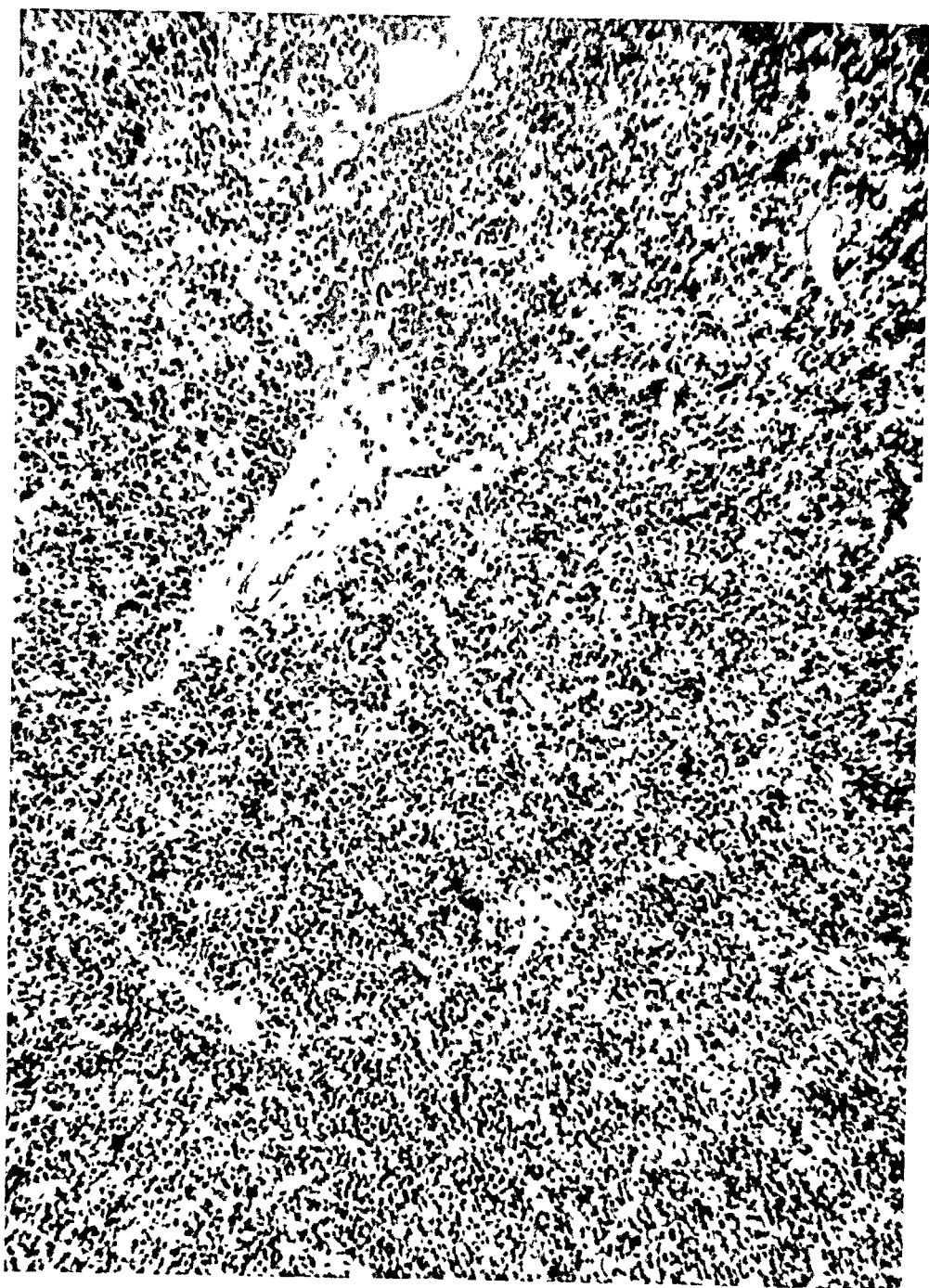


FIG. 9a.

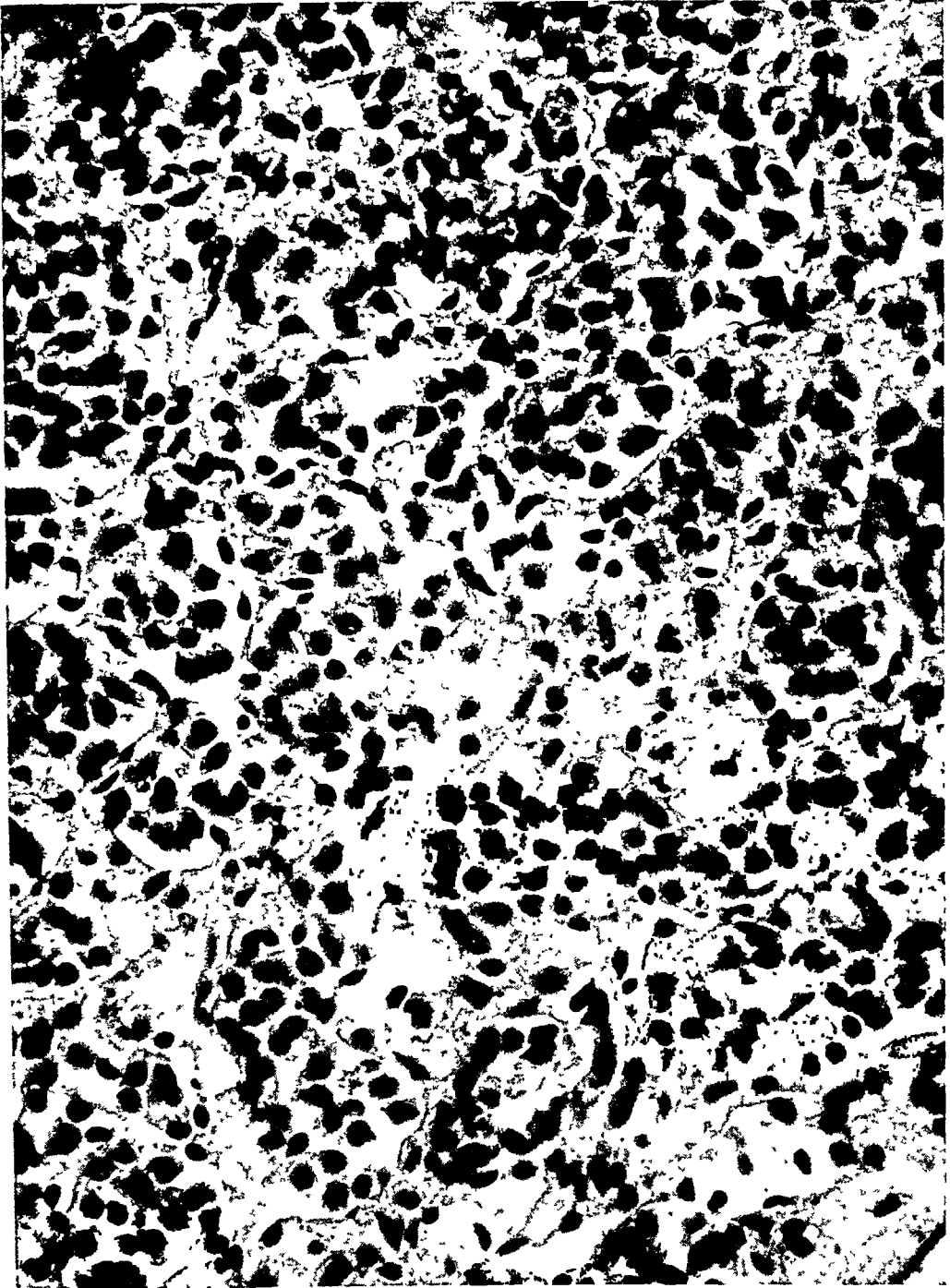


FIG. 9b.

FIG. 9a and b. Low power and high power views of a section of thyroid tissue from a cretinous pig, a companion to the one whose thyroid is shown in figure 8. Note the solid structures characteristic of fetal adenoma.

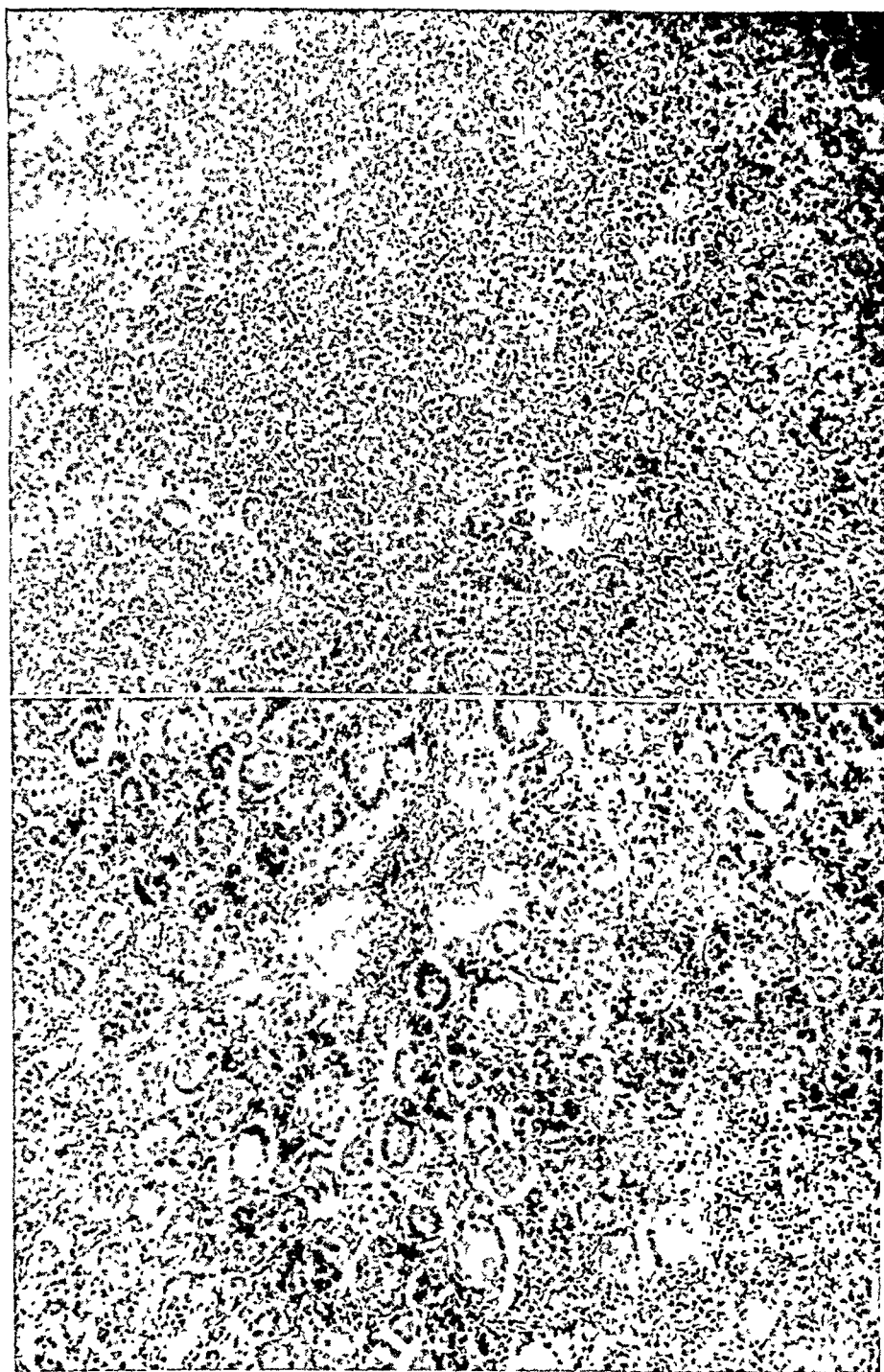


FIG. 10. Two low power views of a section of thyroid from a thyrotoxic patient who had received thiouracil for 10 months.

However, when both drugs were fed simultaneously, seven of 10 rats developed adenomata and the remaining three carcinomata of the thyroid.

The production of thyroid carcinomata under these experimental conditions raises certain practical problems relative to the dangers of using thiouracil in the treatment of hyperthyroidism. As the editorial⁶ in the *Journal of the American Medical Association* suggests, might not the prolonged use of thiouracil in susceptible individuals lead to the development of clinical cancer of the thyroid? As yet there is no answer to this question based on experience with patients, but it certainly should cause one to be cautious in the use of thiouracil except as a preliminary medication in preparing the patient for thyroidectomy.

SUMMARY

1. Two cases of sporadic cretinism with goiter are presented together with biochemical and pathological studies.

2. Evidence for a possible relationship between hyperplasia and neoplasia of the thyroid gland is discussed.

BIBLIOGRAPHY

1. HAMILTON, J. G., SOLEY, M. H., REILLY, W. A., and EICHORN, K. B.: Radioactive iodine studies in childhood hypothyroidism, *Am. Jr. Dis. Child.*, 1943, lxvi, 495.
2. RAWSON, R. W., TANNHEIMER, J. F., and PEACOCK, W.: The uptake of radioactive iodine by the thyroids of rats made goiterous by potassium thiocyanate and by thiouracil, *Endocrinology*, 1944, xxxiv, 245.
3. MARINE, D., and LENHART, C. H.: The pathological anatomy of the human thyroid gland, *Arch. Int. Med.*, 1911, vii, 506.
4. HELLWIG, C. A.: Thyroid adenoma in experimental animals, *Am. Jr. Cancer*, 1935, xxiii, 550.
5. BIELSCHOWSKY, F.: Tumours of the thyroid produced by 2-acetylaminofluorene and allylthiourea, *Brit. Jr. Exper. Path.*, 1944, xxv, 90.
6. Editorial: Thiourea and experimental carcinogenesis in the thyroid, *Jr. Am. Med. Assoc.*, 1945, cxxvii, 278.

AN INQUIRY INTO THE INCIDENCE OF HYPER-HIDROSIS IN CONVALESCENT TRENCH FOOT *

By JACOB J. SILVERMAN, Major, M.C., A.U.S., *Staten Island, N. Y.*

THE statement is sometimes made that in the later stages of trench foot one of the frequent complaints is excessive sweating of the feet. As far as can be learned from the literature no attempt has ever been made to study this phenomenon in trench foot to determine its exact incidence. Ungley and Blackwood¹⁸ divided the clinical course of trench foot into three stages: (1) Prehyperemic stage of a few hours to several days. In this stage the feet are cold, dry, swollen, numb and discolored. (2) Hyperemic stage of six to 10 weeks. In this stage the feet are swollen, anesthetic, red and warm. Sweating is frequently absent and seems to coincide with the sensory loss. (3) Posthyperemic stage lasting from weeks to months. Raynaud-like phenomena may be found in this stage, and on exercise there is early pain and swelling. In spite of the tissue damage which may be extensive, the peripheral pulse is palpable and of good quality.⁸ According to Ungley and Blackwood, in the posthyperemic stage, "there are often complaints of excess sweating or of sweat rashes; on a hot day socks are quickly soaked, but extremities may sweat heavily even when cold."

Soldiers suffering from trench foot who are evacuated to the United States are usually in the posthyperemic stage. An opportunity, therefore, presented itself at this General Hospital to study the sweat response of the feet in soldiers suffering from convalescent trench foot. Two hundred soldiers were studied and they were all from the European theater of operation. The study was limited to white soldiers whose average age was 25. The majority of the patients came from infantry units. There was an average interval of four months from the time of the onset of the condition to the date of this study. Each soldier was convalescing from either a moderate or an advanced type of trench foot. A moderate type was characterized by a typical history of exposure with skin and soft tissue changes but without evidence of gross gangrene. An advanced type was characterized by gangrene with subsequent loss of foot substance. There were 100 patients of each type in this study. For comparative purposes the sweat response was also studied in 100 patients from the general medical wards. This last group was made up of patients suffering from arthritis, malaria, valvular heart disease, hypertension, and the usual run of psychoneurosis seen on general medical wards. No patient in this last group gave a history of trench foot or symptoms from exposure to unusual cold or dampness.

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From the Cardiovascular Section, U. S. Army General Hospital, Camp Butner, N. C. Colonel Roy H. Turner, Surgeon General's office, arranged for this study.

TECHNIC

To study the sweat response the technic of Silverman and Powell¹² was used. A brief description of the technic will suffice for present purposes. A 25 per cent solution of tincture of ferric chloride is applied to the sole of the foot. After drying, contact is made for a specified time on specially prepared tannic acid paper. Sweat is approximately 99 per cent water and will carry with it in solution the readily soluble ferric chloride. The tannic acid paper reacts with the soluble iron to form a stain. Prints are obtained on the paper which vary in intensity depending upon the amount of sweating. For purposes of this study, three types, depending on the degree of sweating, have been classified: (1) faint response; (2) moderate response; (3) intense response. Examples of the three types are shown (figure 1). To correlate

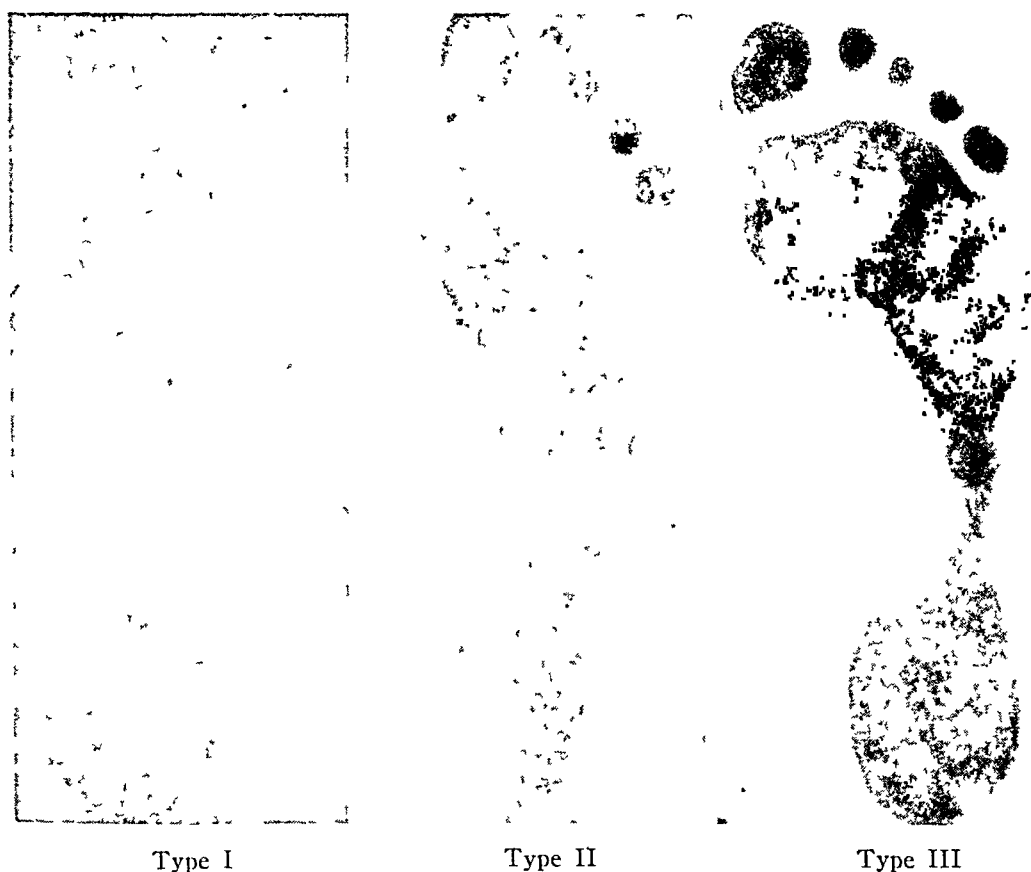


FIG 1. Type I, faint response; Type II, moderate response; Type III, intense response. Classification used in the study of the sweat response of the sole of the foot

the sweat response of the sole with the palm, sweat patterns of the palm and sole were taken simultaneously on the same patient. A similar technic was applied to the palm and the same classification was used (figure 2). The study was carried out by trained enlisted personnel in a quiet, comfortable room, free from distracting influences. To check the results, the tests were frequently repeated on the same patient.

FINDINGS

Chart 1 illustrates the type of sweat response of the soles of the foot found in the three groups. A type 3, or intense response, was found in 18

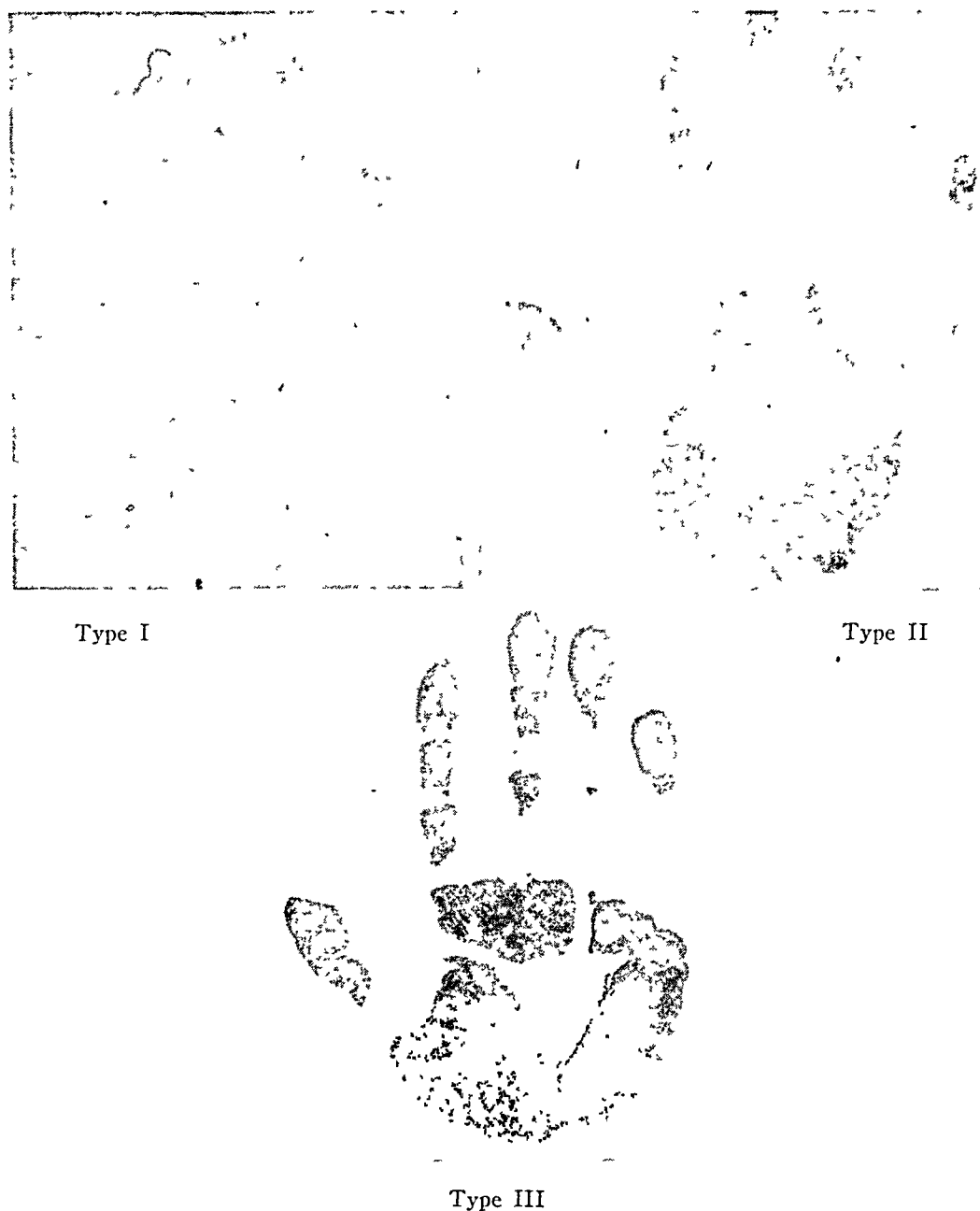


FIG. 2. Type I, faint response; Type II, moderate response; Type III, intense response. Classification used in the study of the sweat response of the palm.

per cent of the moderate trench foot patients, 17 per cent of the advanced trench foot patients, and 23 per cent of the general medical patients. The degree of trench foot involvement, therefore, had no bearing on the inci-

dence of excessive sweating. More interestingly, a slightly higher incidence of excessive sweating of the soles was found in the group of medical patients who gave no history of trench foot. The results of the study of the sweat response of the palm are shown in chart 2. There was an almost identical incidence of the sweat responses of the palms in the two types of trench foot. The general medical patients, however, showed a striking increase in the excessive sweat response of the palm. Whereas 36 per cent of the trench foot cases gave an intense response of the palm, 59 per cent of the general medical patients gave this same type of response.

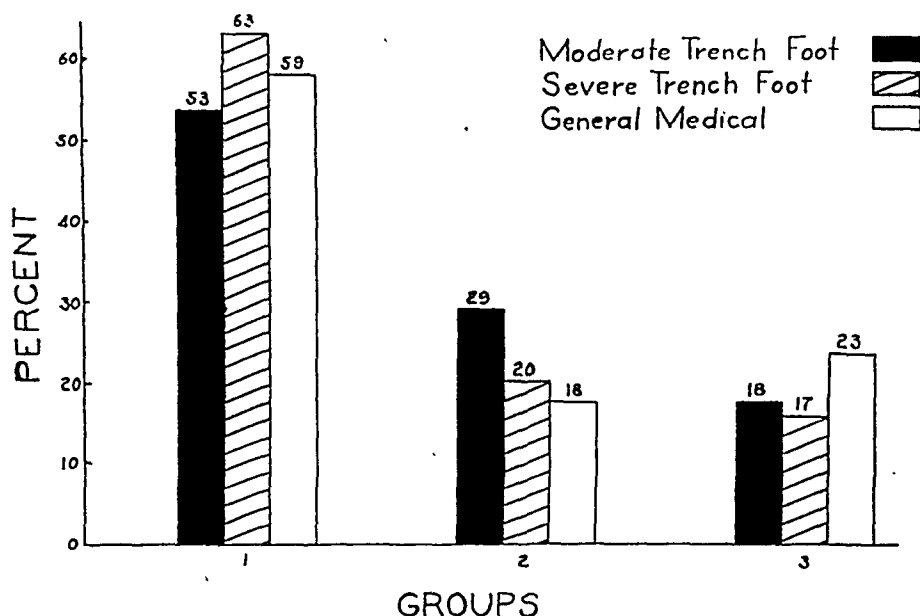


CHART 1. Comparative sweat response of the soles of the feet in 100 moderate trench foot patients, 100 severe trench foot patients, and 100 general medical patients without trench foot. Classification: 1, faint response; 2, moderate response; 3, excessive response.

Sweat patterns of the palms and soles were taken simultaneously but the figures are not shown. Of the 18 patients with moderate trench foot who gave a type 3 or intense sweat response of the sole, 14 demonstrated at the same time an intense response of the palm. There were 17 patients of the severe trench foot group with an intense sweat response of the sole, and 13 of these gave a similar sweat response of the palm. In the general medical patients, there were 23 with an intense sweating response of the soles and all these same patients simultaneously showed an intense response of the palms. In brief, where there was excessive sweating of the foot, the same type of response was almost invariably recorded for the palm, regardless of the diagnosis or degree of trench foot.

It did not follow, however, that a dry type of foot was accompanied by a dry palm. There were 53 patients with moderate trench foot who gave a type 1 or faint response of the soles, and of these only 26 gave a similar response of the palms. In the severe trench foot cases there were 63 patients

with a faint response of the soles, and of these, 60 gave a faint response of the palms. There were 59 patients in the general medical group who showed a faint response of the soles and of these, only 23 simultaneously showed a similar response of the palms. It is interesting to note, the more severe the trench foot, the higher the incidence of type 1 or faint response of the sole.

Reversing the procedure and using the palm as a guide to the type of sweating of the foot, the following figures were obtained. In the group of patients with moderate trench foot, there were 36 patients with excessive sweating of the palm, 14 of whom simultaneously showed excessive sweating

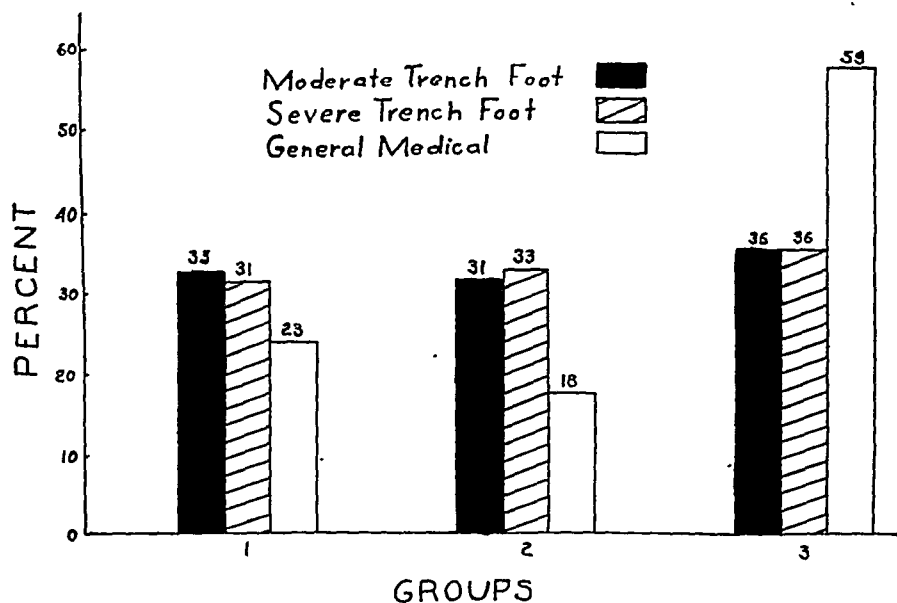


CHART 2. Comparative sweat response of the palms in 100 moderate trench foot patients, in 100 severe trench foot patients, and 100 general medical patients without trench foot. Classification: 1, faint response; 2, moderate response; 3, excessive response.

and 11 faint sweating of the soles. In the same group of patients there were 33 with a faint palmar response and of this group 26 gave a faint response of the soles. In the severe trench foot cases there were 36 patients with excessive sweating of the palms, 13 of whom gave a faint response of the soles. In this same severe group of trench foot there were 31 patients who gave a faint response of the palms and of this group, 30 gave a faint response of the soles. Studying the general medical patients, there were 59 patients who gave an excessive sweat response of the soles, while 21 showed a faint response of the soles. In this same general medical group, there were 23 patients who gave a faint response of the palm and these entire 23 simultaneously also gave a faint response of the soles. In brief, a dry palm was almost invariably accompanied by a dry sole, regardless of the type of trench foot or medical diagnosis. As the sweat of the palms increased, the sweat of the soles also increased but to a lesser degree.

DISCUSSION

Sweating of the soles and palms is unique and differs from general body sweating on anatomic and physiologic grounds.¹³ Anatomically, there are more sweat glands on the palm and sole than anywhere else on the general body surface.⁷ The sweat glands on the palms and soles are arranged on ridges which assume characteristic patterns. This arrangement assures maximum grasping and tactile facility.⁵ Sweating in these locations takes place continuously; whereas, on the general body surface it is intermittent.⁶ Under ordinary conditions, sweating of the palms and soles is not influenced significantly by the outside temperature.⁹ Increasing the outside temperature will augment general body sweating but not sweating of the palms or soles. Finally, the palms and soles reflect emotional changes.³ In relaxed states, such as in sleep, the palms and soles are characteristically dry, regardless of the outside temperature. In states of apprehension and tension the palms and soles perspire profusely. Excessive palmar sweating seen in anxiety states is a well known clinical phenomenon.¹⁴

In dealing with observations on sweating, one must, therefore, be careful to differentiate sweating of the palms and soles from general body sweating. It should be emphasized, the observations in this study were confined to the palms and soles. Preliminary studies of general body sweating in the trench foot patients were also carried out.* The trench foot patients, together with controls, were placed in an experimental environment in which the temperature was gradually raised. As the temperature was raised, sweating increased generally over the entire body, except for the soles and palms. The dorsum of the feet and hands shared equally in the increased sweating. Exercise caused a similar response. No significant difference of excessive sweating of the general body was found between the trench foot patients and the controls.

It may logically be asked why the palms and soles failed to give identical responses in all patients. Normally, sweating of the soles and palms behaves as a similar mechanism; quantitatively, however, there is a significant difference. Careful measurements have shown that the rate of water loss in the toetips is approximately one-half to two-thirds that in the fingertips.^{2, 11} With slight sweating of the palms this difference is not noticeable. The difference becomes more apparent as the stimulus for this type of sweating is increased and can be demonstrated by the technic used in this study.

Cold causes an inhibition of sweating both locally and reflexly. A variety of pathologic changes has been described in trench foot.⁴ The skin, being the most exposed organ, is one of the first to react to cold. Most of the observations, however, have been confined to blood vessels, nerves, muscles, and connective tissue beneath the skin. Degenerative changes in the sweat glands have been noted. More important, perhaps, from a sweating standpoint, are the changes seen in the nerve endings.^{1, 4} Sweat-

* A recently described colorimetric technic¹⁵ was used to record this type of sweating.

ing behaves as a cholinergic mechanism; on anatomic grounds, however, the sweat fibers travel along a sympathetic pathway and are contained in the peripheral nerves. Severance or destruction of this pathway leaves the innervated part anhydrotic. Clinically, the early symptoms of nerve involvement in trench foot are striking.¹⁷ At first there is an uncomfortable sensation of coldness followed by numbness. There may be some paresthesias and vague aches and pains in the arches and ankles. The patients frequently complain of clumsiness and describe their sensations as "walking on blocks of wood." The feet may be anesthetic to pain, touch, and temperature. There is anhidrosis and this follows rather closely the disturbance in sensation. As improvement occurs, one of the early signs observed is a return of the sweating.¹⁸ The return of the sweating function will depend to a great degree on the recovery of the damaged nerve endings. If any changes in the sweat mechanism are to be predicted in severe trench foot, a picture of relative anhidrosis rather than hyperhidrosis should be expected.

In a recent study of the casualties of the Attu campaign, Lesser¹⁰ pointed out that the status of the vasomotor disturbances frequently seen in immersion foot (a condition closely allied to trench foot) is indefinite and difficult to evaluate. In Lesser's series there were two groups of patients. The first group presented severe gangrene and loss of foot substance. Excessive sweating was not a feature in this group; these patients seemed to show few signs and symptoms of a vasomotor imbalance. The second group, those without tissue loss, presumably the milder cases, was characterized by a high incidence of vasomotor imbalance. These milder cases complained of coldness and excessive sweating of the feet. Repeated lumbar sympathetic novocaine blocks in this second group gave disappointing results. Lesser felt that the difference in the two groups may be related to a "constitutional sympathetic nervous system instability of the individual patients."

The milder trench foot patients, those without gangrene or tissue loss, formed by far the largest group evacuated to general hospitals in the United States. The complaints of many of these patients were often entirely out of proportion to the findings on examination. Trench foot, like any other somatic disorder, has psychogenic components which may modify and color the underlying condition. It is generally agreed that, given the necessary conditions of coldness, dampness, immobility, fatigue, improper hygiene and lack of proper footgear, trench foot can occur in any soldier. Moreover, in trench foot, the anxiety state may be one of the predisposing factors in its development. One of the cardinal principles in the prevention of trench foot is the matter of keeping the feet dry. However, in severe anxiety states, it is practically impossible to keep the feet dry, for like palmar sweating, it is continuous and excessive. It is interesting to note that in many of our patients with trench foot we have been able to elicit a history indicating a high incidence of excessive sweating of the palms and soles, even before induction.

As stated above, sweating of the palms and soles is continuous and occurs normally. The average patient is not aware of this phenomenon and particularly is not observant as to the amount of sweating. With the development of trench foot, however, any sign or symptom relating to the foot takes on added significance. A soldier returning with a diagnosis of trench foot may be unusually apprehensive, not only about his feet but also about many other problems. He hears all kinds of rumors. Naturally, he is concerned when he hears that trench foot leads to loss of toe or limb. Excessive sweating in such a patient should not be unusual. Furthermore, many of these patients have been harboring fungous conditions of their toes and feet. "Athlete's foot" and excessive sweating are frequently seen together and both tend to aggravate each other. It is surprising how many patients attribute both conditions to trench foot.

As Scoville¹⁰ pointed out, trench foot, like low back pain, is a condition which easily lends itself to the development of a neurosis. The onset is dramatic, and the complaints, especially in the milder cases, are difficult to evaluate. The medical officer at first had little or no experience with trench foot. The emphasis was on conservatism and hospitalization was often prolonged. It was easy, therefore, for many patients to capitalize on the situation. Furthermore, the diagnosis of trench foot has an emotional appeal which is socially acceptable to the neurotic. Trench foot is a mark of a fighting soldier. Many a severe anxiety problem has been evacuated to the United States camouflaged under a diagnosis of trench foot.

That the excessive sweating of the feet seen in patients with trench foot is not purely a local manifestation but part of a generalized process is attested by the following facts. Patients with unilateral involvement showed no higher incidence of hyperhidrosis in the affected extremity than in the uninvolved extremity.¹⁶ Secondly, the severity of trench foot had no bearing on the incidence of hyperhidrosis. In fact, those with the severer type of trench foot had, if anything a tendency toward a drier foot. Furthermore, when the trench foot patients were compared with the general medical patients, a slightly higher incidence of hyperhidrosis was found in the latter group, particularly those with functional complaints. Finally, in those patients who complained of excessive sweating of the feet, invariably there was excessive sweating of the palm and often of the axillae. These are the locations for emotional sweating. Where there was a dry palm there was practically always a dry foot, regardless of the type of trench foot or medical diagnosis.

SUMMARY

1. An attempt was made to study the incidence of hyperhidrosis in 200 patients convalescing from varying degrees of trench foot, and the findings were compared with 100 general medical patients without trench foot. The degree of trench foot seemed to have no bearing on the incidence of

hyperhidrosis. The general medical patients showed a slightly increased incidence of hyperhidrosis.

2. The hyperhidrosis seen in trench foot is part of a generalized process similar to that seen in an anxiety state.

3. Hyperhidrosis is not a diagnostic feature of convalescent trench foot. In a patient convalescing from trench foot the complaint of excessive sweating of the feet should invite investigation for other causes of hyperhidrosis.

BIBLIOGRAPHY

1. BLACKWOOD, W.: Studies in the pathology of human 'immersion foot,' Brit. Jr. Surg., 1943-4, xxxi, 329.
2. BURCH, G. E., COHN, A. E., and NEWMANN, C.: A study of the rate of water loss from the surface of the fingertips and toetips of normal and senile subjects and patients with arterial hypertension, Am. Heart Jr., 1942, xxiii, 185.
3. DARROW, C. W.: Neural mechanism controlling the palmar galvanic skin reflex and palmar sweating: A consideration of available literature, Arch. Neurol. and Psychiat., 1937, xxxvii, 641.
4. FRIEDMAN, N. B.: The pathology of trench foot, Am. Jr. Path., 1945, xxi, 387.
5. JONES, F. W.: The principles of anatomy as seen in the hand, 1942, Williams & Wilkins, Baltimore.
6. JURGENSEN, E.: Mikrobeobachtungen der Schweißsekretion der Haut des Menschen unter Kontrastfärbung, Deutsch. Arch. f. klin. Med., 1924, cxliv, 193.
7. KRAUSE: Wagner's Handwörterbuch der Physiologie, 1844, ii, 131. (Cited by Kuno.⁹)
8. KRAUSE, L. A. M., WALLACE, J. J., and SILVERMAN, J. J.: The incidence of palpable pulsations in convalescent trench foot, Am. Jr. Med. Sci., 1946, ccxi, 729.
9. KUNO, Y.: The physiology of human perspiration, 1934, J. & A. Churchill, London.
10. LESSER, A.: Report on immersion foot casualties from the battle of Attu, Ann. Surg., 1945, cxxi, 257.
11. NEUMANN, C., COHN, A. E., and BURCH, G. E.: A quantitative method for the measurement of the rate of water loss from small areas, with results for the fingertip, toetip and postero superior portion of the pinna of normal resting adults, Am. Jr. Physiol., 1941, cxxxii, 748.
12. SILVERMAN, J. J., and POWELL, V. E.: Studies on palmar sweating, I. A technique for the study of palmar sweating, Am. Jr. Med. Sci., 1944, ccviii, 297.
13. SILVERMAN, J. J., and POWELL, V. E.: Studies on palmar sweating, II. The significance of palmar sweating, Am. Jr. Med. Sci., 1944, ccviii, 298.
14. SILVERMAN, J. J., and POWELL, V. E.: Studies on palmar sweating, III. Palmar sweating in an army general hospital, Psychosom. Med., 1944, vi, 243.
15. SILVERMAN, J. J., and POWELL, V. E.: A simple technic for outlining the sweat pattern, War Med., 1945, vii, 178.
16. SILVERMAN, J. J.: Unpublished data.
17. Trench Foot, TB Med., 1944, 81, U. S. Army Med. Dept. (abstracted Bull. U. S. Army Med. Dept., 1945, iv, 265).
18. UNGLEY, C. C., and BLACKWOOD, W.: Peripheral vasoneuropathy after chilling, Lancet, 1942, ii, 447.
19. WHITE, J. C., and SCOVILLE, W. B.: Trench foot and immersion foot, New England Jr. Med., 1945, ccxxxii, 415.

ON THE TOXICITY OF THE MERCURIAL DIURETICS: OBSERVATIONS ON EIGHTEEN CASES WITH SUGGESTIONS FOR THE PREVENTION OF TOXIC REACTIONS *

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SINCE the introduction of novarsurol as a diuretic by Saxl and Heilig¹ in 1923, dehydration by means of the mercurial has played an important rôle in the treatment of congestive heart failure. Within recent years, however, instances of fatal and non-fatal reactions have been described in the literature. These reactions, though they occur infrequently, cause a great deal of apprehension when one has to resort to the use of the drug.

The literature on the toxic reactions to the mercurial diuretics published prior to 1942 has been adequately reviewed by DeGraff and Nadler.² In 1944, Wexler and Ellis³ reported two more cases with fatal and nine cases with non-fatal reactions. The following year, Volini, Levitt, and Martin⁴ described three instances of sudden death following mercurial diuresis. Another fatality was also reported in the same year by the author.⁵

In spite of the increasing number of clinical reports and the abundant experiments on animals, the explanations for these toxic effects are as yet speculative. The literature indicates widely varying opinions concerning their mechanism. Observations, either clinical or laboratory, should be of value in elucidating their pathogenesis and thus establishing a firmer basis for the therapy of congestive heart failure.

The purpose of this report is to record observations on the toxicity of the mercurial diuretics in 18 patients in the hope that these observations may throw further light on the mechanism of the reactions as well as on the methods of their prevention.

GENERAL CONSIDERATIONS

Incidence. Considering the extensive use of the mercurial diuretics, the number of serious reactions reported from their use is very small. DeGraff and Nadler² state that approximately 6000 injections of mercupurin have been given each year in Bellevue Hospital since 1934, with no serious toxic reactions or deaths that may be attributed to the drug. The two fatal cases reported by Wexler and Ellis³ occurred in a series of 5,200 injections during a six-month period. The 18 cases comprising this report occurred in a five-year period. The number of injections during this period can not be determined.

* Received for publication December 14, 1945.

From the medical departments of the Medical Center, the Fairmount Hospital, and the Greenville Hospital, Jersey City.

Although statistical data are not available, the frequency of mild reactions is probably greater than that of fatal reactions. In general, it can be stated that the incidence of toxic reactions following the mercurial diuretics is probably lower than that of other drugs used with equal frequency.

Pathogenesis. There are a number of theories to explain the mechanism of these reactions. The fact that some fatalities occurred in cases in which previous injections did not produce any reactions has led Greenwold and Jacobson⁶ to consider them as anaphylactic in nature. The previous injections, they believe, might have sensitized the patient to the mercury ion. This theory, however, does not explain the fatalities that have occurred after the first injection.

Another explanation for the toxic manifestations is that it is due to a direct action of the mercurial diuretic on the heart muscle. This theory receives support from some laboratory and clinical evidence. Salant and Kleitman⁷ were the first to observe ventricular fibrillation in normal dogs following the intravenous administration of inorganic mercurial salts. Later Jackson⁸ demonstrated that fibrillation and death could be produced in normal dogs by the intravenous injections of 5 c.c. of a 2 per cent solution of salyrgan. Chastain and Mackie⁹ also showed that esidrone injected intravenously in normal dogs will produce changes in the electrocardiogram followed by ventricular flutter, fibrillation and death. By injecting normal dogs with various mercurial compounds, Barker, Lindberg and Thomas¹⁰ obtained changes in the T-waves, runs of extrasystoles, ventricular tachycardia, ventricular fibrillation and death. In two of the fatal cases described by Volini, Levitt, and Martin,⁴ the electrocardiogram showed the development of ventricular fibrillation. In one case there were changes in the ST junction, the ST interval, and also in the T-waves. The electrocardiogram in a non-fatal case described in this report showed changes in the ST segment followed by ventricular premature systoles and ventricular paroxysmal tachycardia. There was normal sinus rhythm when the patient recovered. We thus have evidence in both the experimental animal and in man that the reaction may be due to a direct effect of the drug on the heart muscle.

Hyman¹¹ believes that the reactions are due to technical rather than hemodynamic factors. The reactions, he states, resemble the syndrome of speed shock in which the blood is rendered non-coagulable when any material is rapidly injected intravenously. From a study on the influence of velocity on the response to intravenous injections, Hirshfeld, Hyman and Wanger¹² state that solutions with larger molecules should be given more slowly than solutions with smaller molecules, and that toxic substances should be given intermittently as well as slowly.

Toxic reactions may also occur as a result of a disturbance in the water and electrolyte equilibrium of the body induced by the mercurial diuretics. Soon after their introduction of novarsurol as a diuretic, Saxl and Heilig¹ showed that diuresis is accompanied by an absolute increase in the chlorides of the urine. Later Crawford and McIntosh¹³ found that the increase in

the chloride excretion in the urine is accompanied by a fall in the serum chloride. Blumgart and his co-workers¹⁴ demonstrated that diuresis is accompanied by an increased secretion of chloride, sodium and potassium. The amount of chloride in the extra urine excreted is greater than that of an equal volume of body fluid. This increased secretion of inorganic ions is accomplished by a relative decrease in tubular reabsorption, the rate of glomerular filtration remaining unaffected. Diuresis is also accompanied by a decrease in the serum chloride concentration which, they believe, is a consequence of the excess urinary chloride loss, and by an approximately equivalent rise in the serum bicarbonate concentration. The serum concentration of sodium and calcium is unchanged.

Chabanier, Lebert, and Lumiere,¹⁵ however, found a drop in the blood sodium and chloride. Keith, Barrier, and Whelan¹⁶ also found increased secretion of sodium following novarsurol in cases of nephritis with edema. The changes in the concentration of the inorganic ions of the blood were inconstant and never marked in degree.¹⁷ Poll and Stern¹⁸ reported seven cases exhibiting toxic reactions to mercurial diuretics which, they believe, were due to a loss of sodium similar to the acute collapse seen in Addison's disease. These inconstant and conflicting findings may be explained by the fact that whereas the mercurial diuretics produce a decrease in tubular reabsorption with no change in glomerular filtration, dehydration produces the opposite effect; i.e., an increased tubular reabsorption and a decrease in glomerular filtration.¹⁹ Hence, the results may vary in different cases and in the same patient at different times.

Lyons and his associates²⁰ have shown that dehydration is accompanied by a fall in the plasma volume associated with a fall in venous pressure and pulse pressure. Coincident with the fall in the plasma volume there is an increase in the serum protein and a rise in the hematocrit reading. As a result of marked hemoconcentration, vascular collapse and death may follow because of a diminished return flow to the heart and a fall in the cardiac output.

Lastly, digitalis toxicity may occur following the administration of the mercurial diuretics as a result of the mobilization of digitalis from the retained tissue fluids. However, this is seldom serious and disappears spontaneously after the cessation of digitalis.

Clinical Manifestations. The reactions may be fatal and non-fatal. Wexler and Ellis⁸ have divided the non-fatal cases into immediate and delayed types. The immediate fatal and non-fatal reactions are characterized by dyspnea, cyanosis or pallor, irregular breathing, drop in blood pressure, cardiac irregularity, unconsciousness and convulsions. Cardiac arrest may occur before respiratory paralysis within five minutes after the injection. Mild non-fatal immediate reactions may be manifested by a sense of apprehension, substernal discomfort, transient dyspnea, orthopnea, cyanosis, sweating and tachycardia. Delayed reactions occur one to two hours after the injection with symptoms of asthma or pulmonary edema. Reactions

may also occur six to 12 hours later with symptoms of weakness, apathy, mental confusion, delirium, coma and death. Hypersensitiveness may present itself with symptoms of fever, erythema, paresthesia and ulcerative stomatitis.

Prevention of Reactions. It is generally stated that there is no known way of avoiding a reaction. The presence of kidney disease is considered a contraindication to the use of the mercurial diuretics, although one may have to resort to their use in spite of impaired kidney function. From experiments on cats, DeGraff and Lehman²¹ conclude that toxic reactions cannot be avoided by dilution of the drug nor by slow injection. Hyman,¹¹ on the other hand, believes that reactions can be prevented by intermittent injections. Barker, Lindberg and Thomas¹⁰ emphasize caution in the intravenous use of the mercurial in a water-logged patient.

It will be apparent from the discussion below that the mercurial diuretics should not be given during a high environmental temperature. Reactions may also be prevented by slow intermittent injections. In one case reactions were prevented by the preliminary injection of sodium thiosulfate.

CLINICAL MATERIAL

The material dealt with in this report has been assembled from three hospitals and comprises 18 cases in which toxic reactions occurred following the intravenous injection of the mercurial diuretics. In no case was there any evidence of impaired kidney function. In 17 cases the reactions were not fatal; in one it was fatal. The latter case, reported elsewhere in detail,⁵ was associated with a high environmental temperature and high humidity. Evidence was presented indicating that the abnormal environmental conditions, causing an increase in the loss of inorganic ions through the sweat glands, were a contributing factor in the cause of death.

In order to determine whether or not there was any correlation between environmental conditions and the toxic reactions in the non-fatal cases, the temperature and humidity at the time of the injections were determined from the United States Weather Bureau. The data as well as other observations will be presented chiefly in tabular form, supplemented by brief summaries of the records of a few illustrative cases.

CASE REPORTS

Case 10. R. H., a 48-year-old man, was admitted to the Fairmount Hospital on March 23, 1943, complaining of dyspnea, orthopnea, cough and swelling of the lower extremities. A known cardiac for the past 18 years, he felt well until 15 months before admission, at which time he began to notice swelling of the ankles and shortness of breath. He had been on a maintenance dose of 0.1 gm. of digitalis and had received four injections of mercupurin and one mercurin suppository before entry without any untoward effect. The last injection was given three weeks before admission to the hospital.

Physical examination revealed peripheral edema, ascites, enlarged liver and distended veins of the neck. The heart was enlarged. The second pulmonic sound was

accentuated. Systolic and diastolic murmurs were heard over the mitral area. The rhythm was totally irregular; the ventricular rate was 108; the radial pulse was 90. The blood pressure was 140 mm. Hg systolic and 80 mm. diastolic. The urine showed a trace of albumin, no sugar, an occasional white cell, and no red cells. The blood count was normal. A chest film showed an enlarged heart with mitral configuration. An electrocardiogram showed auricular fibrillation and right axis deviation. The diagnosis was rheumatic heart disease, mitral stenosis, mitral regurgitation, enlarged heart, auricular fibrillation and congestive heart failure.

Under rest and 0.1 gm. of digitalis daily he improved but the edema persisted. On the third day after admission, the patient was given intravenously 2 c.c. of mercupurin. About two minutes later he became pale, sat up in bed and complained of marked palpitation. The respirations became labored and the ventricular rate increased to 168, the pulse rate to 144. The blood pressure was 90 mm. Hg systolic and 60 mm. diastolic. The reaction lasted about three minutes and the patient recovered spontaneously. A diuretic response of 3500 c.c. resulted.

The peripheral edema, however, returned and it was found necessary again to resort to mercupurin. The patient refused any but the intravenous method. After an interval of 10 days, 2 c.c. of mercupurin were given slowly and intermittently at a rate of 0.1 c.c. every 15 seconds. There was no reaction after the injection. Four subsequent injections given with the same technic produced no untoward effects. He died of congestive failure eight weeks after the reaction.

Case 16. M. F., a 62-year-old female, entered the Medical Center on July 9, 1944, because of palpitation, dyspnea and peripheral edema of six months' duration. She had been on a maintenance dose of 0.1 gm. of digitalis and received eight injections of mercupurin without any untoward results.

Physical examination revealed peripheral edema, ascites, enlargement of the liver and distended veins of the neck. The heart was enlarged to the left. A systolic thrill was felt over the aortic area. The second aortic sound was absent. A loud rough systolic murmur was heard over the aortic area and a soft diastolic murmur over the left sternal border. There was a small Corrigan pulse. The blood pressure was 140 mm. Hg systolic and 60 mm. diastolic. The Wassermann reaction was negative. The urine showed a trace of albumin, a trace of sugar and a specific gravity of 1.022. The blood count showed 4,260,000 red cells and 7,200 white cells. The differential count was normal. The non-protein nitrogen was 38 mg., sugar 126 mg. per 100 c.c. of blood. An electrocardiogram showed a regular sinus rhythm, depressed ST₁ and ST₂, and left axis deviation. Roentgen examination revealed cardiac enlargement, moderate widening of the aorta, with dancing aortic calcifications. The diagnosis was etiology unknown, calcific aortic stenosis, aortic insufficiency, enlarged heart, regular sinus rhythm and congestive heart failure.

She improved under rest, digitalis, and limitation of fluids. Mercupurin was given first once a week and later once in two weeks. The environmental temperature during the entire period between August 10 to August 17 was exceedingly high, the daily maximum temperature ranging from 92° F. to 96° F. She was given 2 c.c. of mercupurin intravenously on August 15. The maximum environmental temperature for that day was 93° F., and the relative humidity varied from 88 per cent to 69 per cent. Six hours after the injection she became restless and was mentally confused. The next day she became more irrational. The skin and tongue were dry. The maximum temperature on that day was 93° F., and the relative humidity ranged from 88 per cent to 98 per cent. She was given salts and fluids were forced. The third day after injection she was still confused and irrational. The temperature on that day again reached a maximum of 93° F., and the relative humidity ranged from 91 per cent to 76 per cent. The same day the non-protein nitrogen was 50 mg., sugar 136 mg., chloride 446.9 mg. per 100 c.c. of blood. The total protein was 9.8 gm. The

carbon dioxide was 55 vol. per cent. The fifth day after injection the symptoms disappeared. The non-protein nitrogen on August 24 was 42 mg., sugar 128 mg., chloride 640 mg. per 100 c.c. of blood. The carbon dioxide was 60 vol. per cent. There were no untoward effects after the subsequent 18 injections. She left the hospital improved 10 months after her admission.

Case 17. B. D., a 53-year-old female, entered the Greenville Hospital on February 23, 1945, because of dyspnea and increasing edema of one year's duration. She gave a history of rheumatic fever at the age of 16. Mercupurin was injected six times before entry; the last injection was given two weeks before entry.

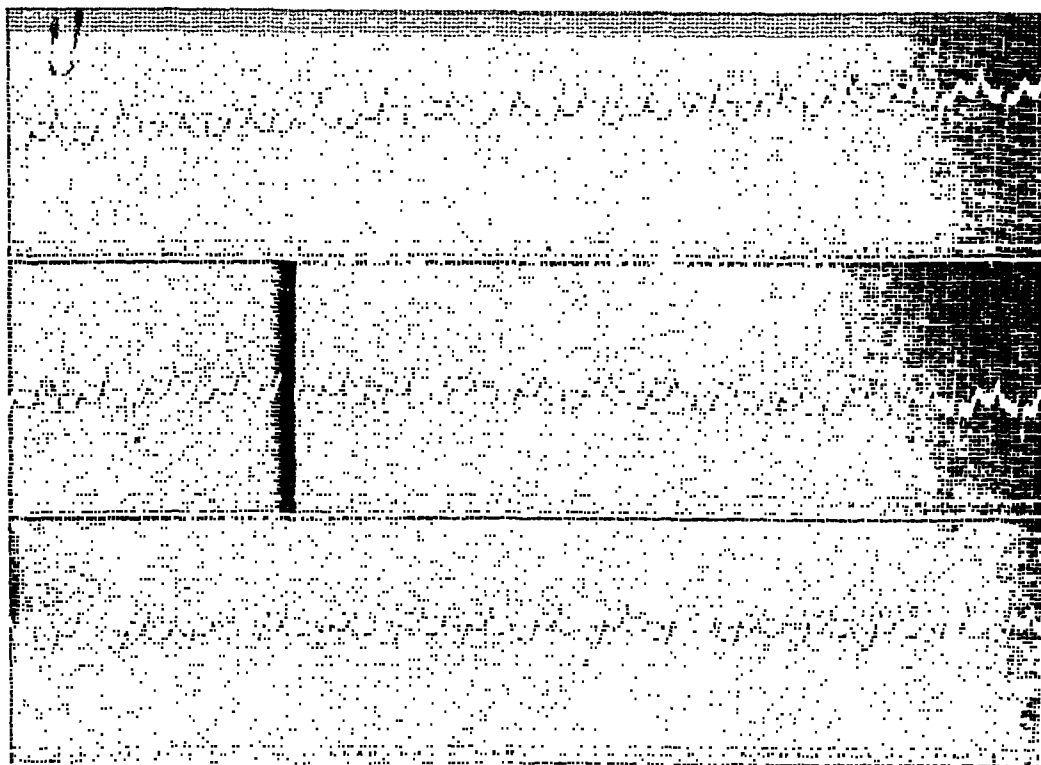


FIG. 1. (*Case 17*). Three portions of the long strip of Lead II, showing alterations in the P-wave, ST segment and the T-wave after injection of mercupurin intravenously. The black line indicates the time of injection. Described in text.

Physical examination revealed distended veins of the neck, peripheral edema, ascites, enlarged liver and congestive râles in both lungs. The heart was enlarged to the left. A systolic thrill was felt over the aortic area. Systolic and diastolic murmurs were heard at the base and apex. The rhythm was regular. There was a small Corrigan pulse. The blood pressure was 210 mm. Hg systolic and 90 mm. diastolic. The urine showed a specific gravity of 1.024, no albumin and no sugar. The blood count was normal. The Wassermann reaction was negative. A roentgenogram of the chest revealed an enlarged heart with mitral configuration and pronounced hypertrophy of the left ventricle. An electrocardiogram showed a regular sinus rhythm, deep S_1 , S_2 , and slightly sagging ST_1 , ST_2 . The P wave was $4\frac{1}{2}$ mm. The PR interval was 0.24 second. The diagnosis was rheumatic heart disease, hypertensive heart disease, aortic stenosis, aortic insufficiency, mitral stenosis, mitral insufficiency, enlarged heart, regular sinus rhythm, partial heart block (prolonged P-R interval) and congestive heart failure.

An intravenous injection of mercupurin was given slowly on the second day of admission. About two minutes later, the patient complained of substernal distress and sat up in bed. The face became pale, the respirations labored and the pulse rapid and irregular. The episode lasted from two to three minutes. A good diuretic effect was obtained, and the patient improved. The edema, however, returned, and it was found necessary to repeat the mercupurin. Since the patient refused any but the intravenous method, that route was again resorted to. An electrocardiogram was taken before the injection; the camera of the machine was shut off just before the insertion of the needle into the vein and the solution was injected slowly but not intermittently with the patient connected to Lead II. A continuous tracing was then

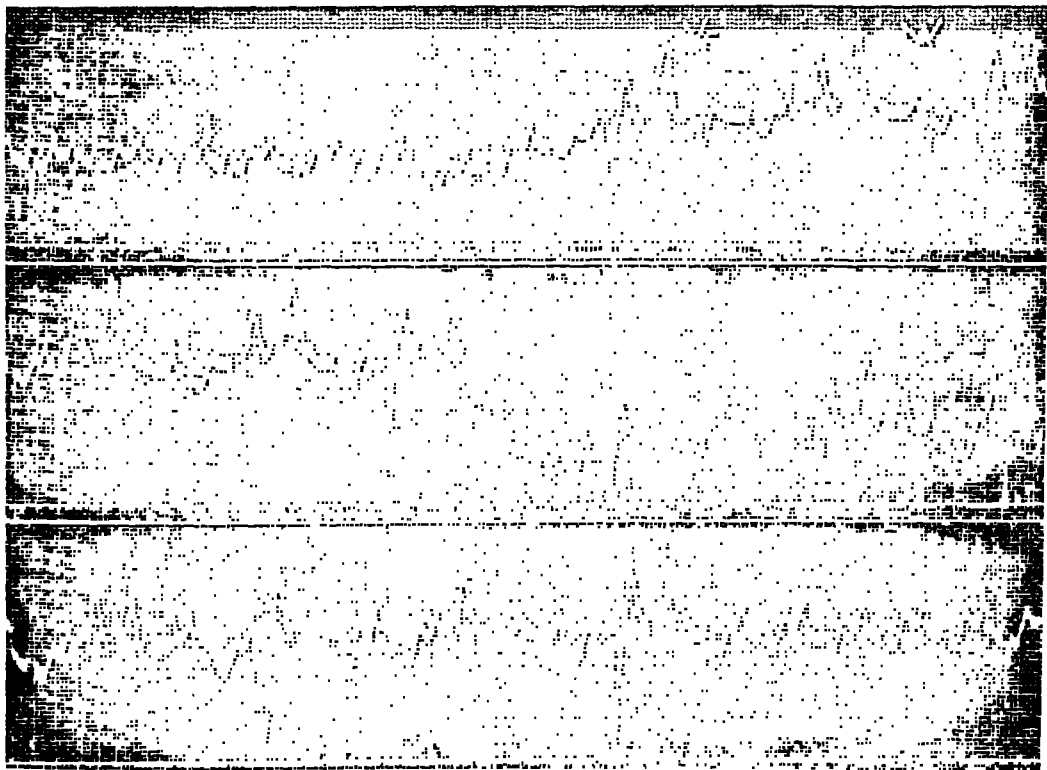


FIG. 2. Continuous tracing of the last strip of figure 1, showing premature ventricular systoles and paroxysmal ventricular tachycardia. V_1 is a ventricular fusion beat. At W, the P-R interval is only .16 second. The A-V junctional tissue has recovered from its relative refractory phase; this is similar to the Wenckebach phenomenon.

obtained in that lead. A reaction similar to that obtained after the previous injection took place 2.6 seconds later. This reaction lasted 2.2 minutes, after which the patient felt better.

Figure 1 shows Lead II before and after the injection. The black line indicates the time of the injection. Figure 2 shows the various later changes in the electrocardiogram after the injection. The first tracing in figure 1 shows a P-wave of $4\frac{1}{2}$ mm., a deep S_{II} , slightly sagging ST_2 and a PR interval of 0.24 second. In the last tracing of figure 1 and in the first portion of the upper tracing in figure 2, the P-wave is only 3 mm.; the ST segment is depressed 2 mm.; T_2 is diphasic. These changes are followed by ventricular premature systoles and later by paroxysmal ventricular tachycardia. The episode lasted 2.2 seconds, after which there was normal sinus rhythm. The ST segment remained depressed, but T_2 became positive.

The following week, the mercupurin, administered slowly but not intermittently, was preceded by 1 gm. of sodium thiosulfate intravenously. There was no reaction after the injection. There were no changes in the electrocardiogram. Two subsequent similar procedures gave the same results. The patient died of cerebral hemorrhage six weeks after the reaction.

DISCUSSION

An analysis of the accompanying table reveals two types of reactions. In the first type, the reaction occurred six to 12 hours after the injection and was characterized by weakness, drowsiness, mental confusion, apathy, restlessness, and in one instance by coma and death. This type comprised 10 cases, eight of which had hypertensive and arteriosclerotic heart disease. One had calcific aortic stenosis and one rheumatic heart disease. The ages ranged from 53 to 71 years. Of the 10 patients, five received ammonium chloride; six patients had previous injections of the mercurial diuretics. In nine instances the mercurials were given under abnormal environmental conditions; the temperature ranged from 91° F. to 99° F., and the relative humidity from 36 per cent to 93 per cent. In one instance, case 12, the maximum temperature was 87° F. and the relative humidity ranged from 36 per cent to 77 per cent. Nine patients recovered with the administration of salt and water. Three of the patients who recovered died eight months to two years later of the usual complications of cardiovascular diseases.

Eichhorst²² in 1898 was the first to note somnolence, disorientation, delirium and apathy following diuresis with digitalis and theobromine sodium salicylate. Srnetz²³ in 1934 noted somnolence and mental confusion following diuresis with salyrgan. Poll and Stern¹⁸ in 1936 described seven cases with similar untoward effects following mercurial diuresis. Three of their patients developed coma and died. These reactions, they believe, were caused by the loss of sodium, resulting from the depletion of sodium chloride reserves of the body.

The reactions in the group described in this report were evidently caused by a disturbance in the water and electrolyte balance in the body resulting from two factors. One factor is the loss of inorganic ions produced by the mercurial diuretics; the other is the loss through the sweat glands as a result of abnormal environmental conditions.

In the second type, the reaction occurred immediately after the injection and was characterized by pallor, cyanosis, substernal distress, palpitation, dyspnea, orthopnea, tachycardia, irregular rhythm, and a fall in blood pressure. The injections were given slowly. The reaction occurred about two to three minutes after the injection, and lasted about two to five minutes. This was noted in eight cases, five of which had rheumatic heart disease, two had hypertensive and arteriosclerotic heart disease, and in one the etiology was unknown. The ages ranged from 35 to 66 years. All patients were in severe congestive failure and had had previous injections of mercupurin. In seven cases the reaction did not occur on subsequent injections when given intermittently.

TABLE I
Toxic Reactions to the Mercurial Diuretics

No.	Case	Age	Date	Diagnosis	Degree of Failure	Dig- italis	Am- mo- nium Chlo- ride	Diuretic and Amt.	No. of Pre- vious Injec- tions	Interval Between Injection and Reaction	Environ- mental Temp. and Humidity	Reaction	Comments
1	M.L.	63	Aug. 21, 1939	Hypertension, arterio- sclerosis, enlarged heart, coronary sclero- sis, myocardial fibrosis, regular sinus rhythm.	+++	Yes	6 gm. per day for 3 days.	Salyr- gan 2 c.c.	None	10 hours	91° F. 93% to 78%.	Weakness, drowsiness, disorienta- tion, stupor.	Recovered with salt and water; died of acute myocardial infarction 24 months after reaction.
2	K.S.	42	Mar. 20, 1940	Rheumatic fever, en- larged heart, mitral stenosis, mitral insuffi- ciency, auricular fibrillation.	+++	Yes	6 gm. per day for 3 days.	Salyr- gan 2 c.c.	5	2 minutes	37° F. 55% to 61%.	Cyanosis, palpitation, dyspnea, orthopnea, tachycardia.	No reaction when the injection was given intermittently. Died suddenly 1½ months after reac- tion.
3	J.L.	71	July 27, 1940	Arteriosclerosis, en- larged heart, coronary sclerosis, myocardial fibrosis, regular sinus rhythm.	++	Yes	No	Mercu- purin 2 c.c.	2	8 hours	99° F. 55% to 61%.	Apathy, drowsiness, stupor, oliguria.	Recovered with salt and water; died of cerebral hemorrhage 16 months after re- action.
4	F.B.	66	May 14, 1941	Arteriosclerosis, hyper- tension, enlarged heart, coronary sclerosis, myocardial fibrosis, auricular fibrillation.	+++	No	No	Mercu- purin 2 c.c.	5	2 minutes	71° F. 58% to 39%.	Palpitation, dyspnea, orthopnea, tachycardia, fall in blood pressure.	No reaction when the injection was given intermittently. Died of congestive failure 2 months after reaction.
5	S.R.	53	June 22, 1941	Hypertension, enlarged heart, regular sinus rhythm.	++	Yes	6 gm. per day for 3 days.	Mercu- purin 2 c.c.	None	12 hours	94° F. 63% to 40%.	Weakness, restlessness, mental con- fusion, stupor.	Recovered with salt and water; died of myocardial infarc- tion 1 year after re- action.

TABLE I—Continued

No.	Case	Age	Date	Diagnosis	Degree of Failure	Digitalis	Ammonium Chloride	Diuretic and Amt.	No. of Previous Injections	Interval Between Injection and Reaction	Environmental Temp. and Humidity	Reaction	Comments
6	L.K.	62	Aug. 9, 1941	Hypertension, arteriosclerosis, enlarged heart, coronary sclerosis, myocardial fibrosis, auricular fibrillation.	++	Yes	No	Mercurin 2 c.c.	None	10 hours	92° F. 73% to 37%.	Drowsiness, weakness, mental confusion.	Recovered with salt and water. In severe congestive failure at this date.
7	B.C.	40	Mar. 18, 1942	Unknown, enlarged heart, auricular fibrillation.	++++	Yes	6 gm. per day for 3 days.	Mercurin 2 c.c.	6	2 minutes	58° F. 60% to 40%.	Pallor, dyspnea, orthopnea, tachycardia.	No reaction when the injection was given intermittently. Died suddenly 1½ months after reaction.
8	M.S.	64	July 20, 1942	Arteriosclerosis, enlarged heart, coronary sclerosis, myocardial fibrosis, regular sinus rhythm.	+++	No	No	Mercurin 2 c.c.	2	12 hours	93° F. 67% to 44%.	Restlessness, mental confusion, delirium.	Recovered with salt and water. Condition unchanged at this date.
9	S.K.	58	Feb. 19, 1943	Hypertension, arteriosclerosis, enlarged heart, coronary sclerosis, myocardial fibrosis, regular sinus rhythm.	++++	Yes	No	Mercurin 2 c.c.	4	3 minutes	48° F. 42% to 38%.	Pallor, dyspnea, orthopnea, tachycardia, fall in blood pressure.	No reaction when the injection was given intermittently. Died of congestive failure 1½ months after reaction.
10	R.H.	48	Mar. 25, 1943	Rheumatic fever, mitral stenosis, mitral insufficiency, enlarged heart, auricular fibrillation.	++++	Yes	No	Mercurin 2 c.c.	4	2 minutes	63° F. 56% to 29%.	Pallor, palpitation, dyspnea, orthopnea, tachycardia, fall in blood pressure.	No reaction when the injection was given intermittently. Died of congestive failure 2 months after reaction.

TABLE I—Continued

No.	Case	Age	Date	Diagnosis	Degree of Failure	Digitalis	Ammonium Chloride	Diuretic and Amt.	No. of Previous Injections	Interval Between Injection and Reaction	Environmental Temp. and Humidity	Reaction	Comments
11	M.B.	45	June 25, 1943	Rheumatic fever, mitral stenosis, mitral insufficiency, enlarged heart, auricular fibrillation.	++	Yes	No	Mercurin 2 c.c.	92	12 hours	96° F. 84% to 36%	Stupor, coma, and death.	
12	W.H.	62	Aug. 1, 1943	Arteriosclerosis, enlarged heart, coronary sclerosis, myocardial fibrosis, regular sinus rhythm.	+++	Yes	6 gm. per day for 3 days.	Mercurin 2 c.c.	None	10 hours	87° F. 77% to 36%	Weakness, delirium, mental confusion.	Recovered with salt and water; condition unchanged at this date.
13	F.K.	55	Aug. 2, 1943	Hypertension, enlarged heart, regular sinus rhythm.	++	Yes	6 gm. per day for 3 days.	Mercurin 2 c.c.	3	11 hours	91° F. 71% to 60%	Weakness, delirium, restlessness, dry tongue.	Recovered with salt and water; condition improved at this date.
14	F.H.	41	May 14, 1944	Rheumatic fever, mitral stenosis, mitral insufficiency, enlarged heart, auricular fibrillation.	++++	Yes	No	Mercurin 2 c.c.	7	3 minutes	78° F. 44% to 87%	Palpitation, cyanosis, dyspnea, orthopnea, tachycardia.	No reaction when the injection was given intermittently. Died suddenly 2½ months after reaction.
15	J.L.	60	July 8, 1944	Arteriosclerosis, hypertension, enlarged heart, coronary sclerosis, myocardial fibrosis, regular sinus rhythm.	++	Yes	6 gm. per day for 3 days.	Mercurin 2 c.c.	None	8 hours	92° F. 78% to 39%	Restlessness, mental confusion.	Recovered with salt and water; condition unchanged at this date.

TABLE I—Continued

No.	Case	Age	Date	Diagnosis	Degree of Failure	Digitalis	Ammonium Chloride	Diuretic and Amt.	No. of Previous Injections	Interval Between Injection and Reaction	Environmental Temp. and Humidity	Reaction	Comments
16	M.M.	62	Aug. 15, 1944	Unknown, calcific aortic stenosis, aortic insufficiency, enlarged heart, regular sinus rhythm.	++++	Yes	No	Mercuripurin 2 c.c.	8	6 hours	93° F. 88% to 69%.	Weakness, restlessness, mental confusion, delirium, dry skin, dry tongue.	Recovered with salt and water; condition improved at this date.
17	B.D.	53	Feb. 25, 1945	Rheumatic fever, aortic stenosis, aortic insufficiency, mitral stenosis, mitral insufficiency, enlarged heart, partial heart block (prolonged P.R. interval), regular sinus rhythm.	+++	Yes	No	Mercuripurin 2 c.c.	6	2.2 minutes	48° F. 59% to 49%.	Substernal distress, pallor, dyspnea, orthopnea, paroxysmal ventricular tachycardia.	No reaction when a preliminary injection of 1 gm. of sodium thiosulfate intravenously was given. Died of cerebral hemorrhage 1½ months after reaction.
18	A.M.	35	June 17, 1945	Rheumatic fever, mitral stenosis, mitral insufficiency, enlarged heart, auricular fibrillation.	+++	Yes	4 gm. per day for 3 days.	Mercuripurin 2 c.c.	5	2 minutes	91° F. 78% to 66%.	Cyanosis, palpitation, dyspnea, orthopnea, tachycardia.	No reaction when the injection was given intermittently. In severe congestive failure at this date.

Case 17 deserves special attention. An electrocardiogram taken during the reaction showed changes in the P-wave, ST segment and the T-wave, followed by ventricular premature systoles and paroxysmal ventricular tachycardia. The patient recovered, and the electrocardiogram returned to normal sinus rhythm. Reactions did not occur after subsequent injections when they were preceded by sodium thiosulfate intravenously. The use of this drug to prevent a reaction suggested itself following the work of Johnston²⁴ who showed that an isolated turtle heart recovered from mercurial poisoning by treatment with sodium thiosulfate. This case differs from the two cases described by Volini, Levitt and Martin⁴ in that the electrocardiograms in their cases showed ventricular fibrillation and the patients died. We thus have electrocardiographic changes in patients exhibiting toxic reactions to the mercurial diuretics similar to those obtained experimentally in animals, indicating that the reaction is due to a direct action of the mercury ion on the heart muscle.

It is noteworthy that seven patients died six to 10 weeks after the reaction. One patient is in severe congestive failure at this writing, two months after the reaction. Apparently, the markedly diseased heart muscle is particularly sensitive to the mercurial diuretic. An immediate non-fatal reaction to a mercurial diuretic should then suggest a poor prognosis.

SUMMARY AND CONCLUSION

1. Reactions to mercurial diuretics in 18 patients are reported.
2. In 10 cases the reaction was delayed and was the result of dehydration. This type of reaction was associated with a high environmental temperature at the time of injection. Nine patients recovered with the administration of salt and water.
3. In eight cases the reaction occurred immediately after the injection. In seven cases reactions did not occur when the injections were given slowly and intermittently. In one case a reaction did not occur when the injections were preceded by sodium thiosulfate intravenously.
4. The occurrence of immediate reactions in a patient under dehydration therapy indicates a poor prognosis.
5. Reactions may be avoided by intermittent injections.
6. Because of excessive dehydration which may follow diuresis and the loss of chlorides through the sweat glands, the mercurials should not be given during a high environmental temperature.

BIBLIOGRAPHY

1. SAXL, P., and HEILIG, R.: Ueber die diuretische Wirkung von Novarsurol und anderen Quecksilberinjektionen, *Wien. klin. Wchnschr.*, 1920, xxxiii, 943.
2. DEGRAFF, ARTHUR C., and NADLER, J. E.: A review of the toxic manifestations of mercurial diuretics in man, *Jr. Am. Med. Assoc.*, 1942, cxix, 1006.
3. WEXLER, J., and ELLIS, L. B.: Toxic reactions to the intravenous injection of mercurial diuretics, *Am. Heart Jr.*, 1944, xxvii, 86.

4. VOLINI, I. F., LEVITT, R. O., and MARTIN, R.: Sudden death following mercurial diuresis, Jr. Am. Med. Assoc., 1945, cxxviii, 12.
5. BEN-ASHER, S.: Fatal reaction following the intravenous injection of mercupurin, Jr. Med. Soc. New Jersey, 1945, xlii, 174.
6. GREENWOLD, H. W., and JACOBSON, S.: Sudden death due to mercurial diuretics, Jr. Pediat., 1937, xi, 540.
7. SALANT, W., and KLEITMAN, N.: Observations on the action of mercury, Jr. Pharmacol. and Exper. Therap., 1922, xix, 315.
8. JACKSON, D. E.: Action of mercury in organic combination, Jr. Pharmacol. and Exper. Therap., 1926, xxix, 471.
9. CHASTAIN, L. L., and MACKIE, G. C.: Studies on toxicity of new mercurial diuretics (sodium salt of pyridine-dicarboxy-mercuri-hydroxyl-propyl-amide-theophyllin), South. Med. and Surg., 1940, cii, 5.
10. BARKER, M. M., LINDBERG, H. A., and THOMAS, M. E.: Sudden death and mercurial diuretics, Jr. Am. Med. Assoc., 1942, cxix, 1001.
11. HYMAN, H. T.: Sudden death after use of mercurial diuretics, communication, Jr. Am. Med. Assoc., 1942, cxix, 1444.
12. HIRSHFELD, S., HYMAN, H. T., and WANGER, J. J.: Influence of velocity on the response to intravenous injections, Arch. Int. Med., 1931, xlvii, 286.
13. CRAWFORD, J. HAMILTON, and MCINTOSH, J. F.: Observation on the use of novarsurol in edema due to heart failure, Jr. Clin. Invest., 1922, i, 333.
14. BLUMGART, H. L., GILLIGAN, D. R., LEVY, R. C., BROWN, M. G., and VOLK, M. C.: Action of diuretic drugs, Arch. Int. Med., 1934, liv, 40.
15. CHABANIER, H., LEBERT, M., and LUMIERE, F.: Analyse physiologique de l'action du 440-B (ou neptal), Bull. Soc. franç. d'urolog., 1927, vi, 259.
16. KEITH, NORMAN M., BARRIER, CHARLES W., and WHELAN, M.: The diuretic action of ammonium chloride and novarsurol in cases of nephritis with edema, Jr. Am. Med. Assoc., 1925, lxxxv, 799.
17. KEITH, N. M., and WHELAN, M.: A study of the action of ammonium chloride and inorganic mercury compounds, Jr. Clin. Invest., 1926, iii, 149.
18. POLL, DANIEL, and STERN, J. E.: Dangers of dehydration treatment in heart disease, Arch. Int. Med., 1936, lviii, 1087-1094.
19. KLINGHOFFER, K. A.: Dehydration from diuretics, New Internat. Clin. (Series 4) 1941, i, 221-226.
20. LYONS, R. H., AVERY, N. L., and JACOBSON, S. D.: Effect of dehydration, produced by mercupurin, on the plasma volume of normal persons, Am. Heart Jr., 1944, xxviii, 247.
21. DEGRAFF, ARTHUR C., and LEHMAN, ROBERT A.: The acute toxicity of mercurial diuretics, Jr. Am. Med. Assoc., 1942, cxix, 998-1001.
22. EICHHORST, H.: Toxämische Delirien bei Herzkranken, Deutsch. med. Wchnschr., 1898, xxiv, 389.
23. SRNETZ, K.: Vorsicht mit Salyrgan bei schwerer Herzschwäche, München. med. Wchnschr., 1934, lxxxix, 1891.
24. JOHNSTON, ROBERT L.: Cardiac depression by mercurial diuretics, Jr. Lab. and Clin. Med., 1941, xxix, 303-307.

CASE REPORTS

EXFOLIATIVE DERMATITIS FOLLOWING PENICILLIN THERAPY *

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ON reviewing the literature we have found no reports of exfoliative dermatitis due to penicillin therapy, hence this report.

Reactions to penicillin, however, are not infrequent and are generally not serious. Kolodny and Denhoff¹ in their study of 124 young men receiving penicillin therapy divided their reactions into the "immediate," those appearing within 24 hours, and the "delayed" which usually occur between seven and 14 days after the initiation of treatment. They report an incidence of 16 per cent "immediate" reactions, characterized by generalized rash, edema, gastrointestinal symptoms and "id" reactions. Seven per cent of all patients developed "delayed" reactions characterized by urticaria, swollen joints, edema, lymphadenopathy, generalized arthralgia, myalgia, and malaise. Flinn, McGee, Featherton, and Kern² in reviewing the literature found an incidence of 3 per cent of mild transient urticaria in patients receiving penicillin. Lyons³ divided the reactions into those associated with penicillin from the same batch, which was thought to represent a reaction from an impurity, characterized by chills, eosinophilia, headache, flushing of the face, muscle cramps, nausea, and vomiting; and those reactions not related to any particular batch of penicillin, characterized by urticaria, fever, transient azotemia, and thrombophlebitis at the site of intravenous administration. Contact dermatitis following handling penicillin during its production and administration has been reported,^{4, 5, 6} as has recurrent vesicular eruptions.⁷ Various allergic manifestations^{8, 9, 10, 11, 12, 13,} have been reported due either to the drug or impurities in the commercial product. A typical urticarial reaction to penicillin consists of multiple wheals, angioneurotic edema, burning and itching of the skin. This usually lasts three to five days, and if the treatment with penicillin is continued the course of the urticaria is supposedly not affected. It has been stated⁸ that if a patient has an urticarial reaction to penicillin on one occasion, he will probably not have this same reaction if penicillin is again used at a later date. Crisp,¹⁴ however, reported a patient who developed urticaria while on penicillin therapy. The drug was then discontinued. Subsequently, on other occasions, penicillin was administered with the development of urticaria. The penicillin used was from different batches. Patch tests were positive. Crisp felt this represented a true allergy to penicillin.

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In addition to these reactions, Morris and Downing¹⁵ report a patient who developed bullous dermatitis. Cormina et al.¹⁰ reported two cases of erythematous vesicular eruption, one with erythema nodosum and one with a transient miliaria eruption, occurring during the treatment of 2000 soldiers on prolonged penicillin therapy. Meads et al.¹⁶ describe the development of a morbilliform skin rash during penicillin treatment.

The following case report illustrates the occurrence of exfoliative dermatitis due to penicillin which to the best of our knowledge has not been previously reported.

CASE REPORT

W. S., colored male, aged 60, was admitted to the hospital complaining of pain in the left anterior chest, of three weeks' duration. This pain was accentuated by deep breathing and movement. The pain was non-radiating and knife-like in character. He had an associated chronic cough which was productive of large quantities of yellow green material. He estimated that he expectorated about 400 c.c. of sputum each 24 hour period. The sputum was not foul smelling. He had lost about 30 pounds since the onset of the illness. He felt weak, tired easily, and had been having a low grade daily fever. The patient also stated he had vague abdominal distress which was not related to his meals and which was not aggravated by any particular type of food. He had never taken alkali for relief of this discomfort. On one occasion the patient passed a large tarry stool at which time he felt weak and faint. This occurred about five weeks before admission.

On physical examination the patient was a well developed and a well nourished colored male who did not appear to be acutely ill. There was limitation of expansion of the left chest. The percussion note at the left base was impaired over an area extending to the level of the fourth thoracic vertebra. The breath sounds were bronchovesicular over this area and numerous coarse moist râles were heard. The blood pressure was 108 mm. Hg systolic and 60 mm. diastolic. The pulse rate was 100. The physical examination was otherwise not contributory.

The laboratory study showed a negative urine. The red blood cell count was 3,480,000 with 71 per cent hemoglobin. The white blood cell count was 15,800 with 78 per cent polymorphonuclear cells. The electrocardiogram was negative. Sputum studies for acid-fast bacilli were negative. Roentgen-ray of the heart and lungs showed an area of heavy infiltration in the midportion of the left lung in an area surrounding the left hilum. There was a large cavity in the center of the opacity, confirming the clinical diagnosis of lung abscess.

A gastrointestinal roentgen-ray series showed evidence of a duodenal ulcer. Cultures of the sputum showed the predominant organisms to be a gram negative diplococcus and a gram negative bacillus.

The patient was placed on postural drainage, sulfadiazine, iron, and a high carbohydrate and high vitamin diet. He improved rapidly. The temperature became normal. His clinical course showed improvement as demonstrated by improved appetite and sense of well being. His sputum decreased and his roentgenogram showed definite improvement with diminution in the size of the abscess cavity. After two weeks sulfadiazine therapy was discontinued and a course of penicillin was started, 15,000 units of penicillin being given every three hours. After the fifth dose of penicillin the patient began to complain of generalized itching of the skin, and a few wheals appeared. The skin became very red over a generalized area. The penicillin was discontinued, and the urticaria and associated skin lesions cleared within 24 hours. Fourteen days later the patient was again placed on a course of penicillin with a dosage of 20,000 units every three hours. After the fourth dose the patient de-

veloped a diffuse erythematous appearance of the skin, he became nauseated and perspired freely. The skin manifestations, although generalized, were more noticeable on the legs, face, neck, and arms. To a lesser degree it was also present over the trunk. This erythematous appearance persisted, although the penicillin was discontinued. No evidence of wheals or urticaria was noted. In about three days, the skin over the involved area began to exfoliate with thin flakes and thickened scales appearing. The scales were a dirty gray color and the underlying skin was red and shiny. This condition persisted, and although it did not become as extensive or as severe as many cases of exfoliating dermatitis, there was still evidence of exfoliation four weeks later. A patch test with this penicillin was strongly positive. Control tests with normal saline were negative. Three weeks later, using a different batch and brand of penicillin, patch and intradermal tests were negative.

COMMENT

No history of a previous fungus infection or treatment with penicillin could be elicited. Before assuming the skin reaction to be the result of some impurity in the penicillin, the findings of Welch and Rostenberg¹⁷ should be considered. They report the occurrence of hypersensitivity of the tuberculin type to crystalline penicillin sodium. In addition, Chow and McKee¹⁸ have reported that the combination of crystalline penicillin and human albumin produces a penicillin-protein complex. It is entirely possible that some of these reactions to penicillin are due to sensitivity to the pure drug itself rather than impurities. However, inasmuch as the first patch test was strongly positive and later patch and intradermal tests, using a different batch and brand of penicillin, were negative, it would appear that the exfoliative dermatitis in this patient was due to some impurity in the original batch of penicillin.

SUMMARY

A case of exfoliative dermatitis following penicillin therapy is presented.

BIBLIOGRAPHY

1. KOLODNY, M. W., and DENHOFF, ERIC: Reactions in penicillin therapy, *Jr. Am. Med. Assoc.*, 1946, cxxx, 1058-1061.
2. FLINN, L. B., MCGEE, L. C., FEATHERTON, W. P., and KERN, D. O.: Skin lesions attending the use of penicillin, *Delaware State Med. Jr.*, 1945, xvii, 133.
3. LYONS, CHAMP: Penicillin therapy of surgical infections in the U. S. Army, *Jr. Am. Med. Assoc.*, 1945, cxxiii, 1007.
4. PYLE, H. D., and RATTNER, HERBERT: Contact dermatitis from penicillin, *Jr. Am. Med. Assoc.*, 1944, cxxv, 903.
5. BINKLEY, G. W., and BROCKMOLE, ARNOLD: Dermatitis from penicillin, *Arch. Dermat. and Syph.*, 1944, 1, 326.
6. BARKER, A. N.: Allergic reactions to penicillin, *Lancet*, 1945, i, 177.
7. GRAVES, W. N., CARPENTER, C. C., and UNANGST, R. W.: Recurrent vesicular eruptions appearing during administration of penicillin, *Arch. Dermat. and Syph.*, 1944, 1, 6.
8. SULLENS, W. E.: Simulating serum sickness reaction to penicillin, *U. S. Naval Med. Bull.*, 1945, xlv, 752.
9. PRICE, I. C.: Severe allergic reactions to intramuscular penicillin, *Canad. Med. Assoc. Jr.*, 1945, liii, 485.
10. CORMINA, F. E., JACOBSEN, L. Y., and SMITH, E. L.: Reactions to penicillin, *Bull. U. S. Army Med. Dept.*, 1945, lv, 694.

11. CRIEP, L. H.: Allergy to penicillin, Jr. Am. Med. Assoc., 1944, cxxvi, 429.
12. PRICE, D. E., McNAIRY, D. J., and WHITE, E. L.: Severe asthma; delayed sensitization to penicillin, Jr. Am. Med. Assoc., 1945, cxxviii, 183.
13. HAILEY, H. E., and MILLARD, E. B.: Foreign protein reaction from penicillin, U. S. Nav. Med. Bull., 1945, xlv, 207.
14. CRISP, L. H.: Allergy, Jr. Am. Med. Assoc., 1944, cxxvi, 429.
15. MORRIS, G. E., and DOWNING, J. G.: Bullous dermatitis, Jr. Am. Med. Assoc., 1945, cxxvii, 711.
16. MEADS, MANSON, HARRIS, H. WILLIAM, and FINLAND, MAXWELL: Treatment of pneumococcic pneumonia with penicillin, New England Jr. Med., 1945, ccxxxii, 747-755.
17. WELCH, HENRY, and ROSTENBERG, ADOLPH, JR.: Hypersensitivity of the tuberculin type to crystalline penicillin sodium, Jr. Am. Med. Assoc., 1944, cxxvi, 10.
18. CHOW, B. F., and MCKEE, CLARA M.: Interaction between crystalline penicillin and human plasma proteins, Science, 1945, ci, 67.

ACUTE SYPHILITIC NEPHROSIS: REPORT OF A CASE*

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FOR many years syphilis has been thought to produce kidney damage, and various renal manifestations have been attributed to this disease. In most of the cases that have been reported, there has been no proof that the *Treponema pallidum* was the direct cause of the kidney damage. Nevertheless, there are several renal syndromes which have been found to be so definitely associated with syphilis that their syphilitic origin is not generally questioned. Of these, the most distinct clinical entity is the acute nephrotic state associated with secondary syphilis. In this syndrome the changes of typical nephrosis occur, but the condition usually clears rapidly, leaving no evidence of persistent renal impairment. Such cases are uncommon, and a review of the literature by Herrmann and Marr¹ reveals that up to 1935 there had been only nine cases reported in which the necessary studies to document the diagnosis had been made. Recently, five additional cases have been described.^{2, 3, 4} Because of the relative rarity of this condition, the following case of acute nephrosis associated with secondary syphilis is reported.

CASE REPORT

D. H., a 31 year old Negress, was admitted to Grady Memorial Hospital because of oliguria, edema and a generalized skin eruption.

Twelve days prior to admission, the patient first noted edema of the face and lower extremities and the onset of a progressive oliguria. Three days later a generalized non-pruritic rash appeared and the lymph nodes in the neck and behind the ears became enlarged. By the time of admission the oliguria had progressed to the extent that the patient was voiding once a day.

For 12 years preceding this illness, the patient had been seen on numerous occasions in the out-patient clinic for minor surgery and prenatal care. During this period there were no symptoms suggesting heart or kidney disease. Her record showed

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repeated urine specimens to be normal, a normal electrocardiogram, and absence of any findings of cardiac or renal damage. Blood pressure determinations varied, with one exception, from 127 to 140 mm. mercury systolic and 90 to 95 mm. mercury diastolic. (A single reading of 160 mm. mercury systolic and 80 mm. mercury diastolic was recorded in the eighth month of pregnancy, but this elevation was not sustained.)

The past history was negative for symptoms or treatment of syphilis. The serologic tests for syphilis had been negative repeatedly and a negative Kahn test had been obtained 18 months before admission.

On admission, the patient's temperature was 99° F. The pulse and respiratory rates were normal and the blood pressure was 128 mm. mercury systolic and 80 mm. diastolic. The face and eyelids showed swelling, and a moderate degree of pitting edema was present in the lower extremities. A dry follicular eruption covered the face, trunk and extremities, but did not include the palms or soles. No mucous membrane lesions were noted in the mouth or nose. The pupils reacted well to light and on accommodation. Ophthalmoscopic examination revealed normal fundi with no changes of the optic discs or retinal vessels. There were firm, discrete, enlarged lymph nodes palpable in the pre-auricular, mastoid, occipital and posterior cervical regions. The lungs were normal to auscultation and percussion; the heart, normal with no murmurs or evidence of enlargement. The spleen and liver could not be palpated. The external genitalia were normal. On speculum examination there appeared a small ulceration of the vaginal mucosa near the cervix. The cervix itself was normal, and examination of the adnexae revealed no masses or tenderness. The deep reflexes were physiologic.

Laboratory Data. The urine on admission contained albumin 4+, with rare red and white blood cells, and many hyaline casts per high power field. Repeated urine examinations during the first few days in the hospital showed a maximum specific gravity of 1.020, albumin 4+, and a few casts. The 24-hour urine specimen contained 4.58 gm. of protein. There was 50 per cent phenolsulfonphthalein excretion in one hour. The hemoglobin was 9 gm. per 100 c.c., and the red blood cell count was 3,900,000 per cu. mm. The white blood cell count was 17,700 per cu. mm. with a slight increase in neutrophils. The sedimentation rate by the Westergren method was 114 mm. in one hour. Blood chemical determinations showed the non-protein nitrogen to be 24 mg. per 100 c.c., cholesterol 109 mg. per 100 c.c., total protein 7.6 gm. per 100 c.c. with 2.6 gm. of albumin and 5 gm. of globulin.

The electrocardiogram was normal and the basal metabolism rate was +14. Teleoroentgenogram of the chest showed slight tortuosity of the aorta, but no cardiac enlargement. Two dark field examinations of serum from the vaginal ulcer revealed no *Treponema pallidum*, but biopsy of the skin showed secondary syphilis. Repeated blood Kahn tests were positive with a titer as high as 800 units.

Treatment and Course. The patient's temperature remained below 99° F. during her hospitalization. Fluids were not restricted, and a high protein diet was given at first, but later this was changed to a low salt diet. Anti-syphilitic therapy was withheld for the first eight days, during which time the patient lost eight pounds in weight. The urine output varied between 1090 c.c. and 1810 c.c. per day. The edema diminished noticeably and the albuminuria decreased from 4+ to 1+ by the nitric acid ring test. The daily total urine protein fell from 4.58 gm. on admission to 0.374 gm. by the eighth day. Casts disappeared from the urinary sediment. The serum cholesterol increased from 109 mg. to 150 mg. per 100 c.c. The follicular eruption showed little, if any, change.

On the ninth hospital day, mapharsen therapy was begun. Doses of 30 mg. were given intravenously three times in the first week and 45 mg. every second day thereafter. There was no Jarisch-Herxheimer reaction. The rash began to subside after three or four days and had almost disappeared by the eleventh hospital day. The

albuminuria continued to decrease, and tests for albumin were all negative after the fourteenth hospital day. The total serum protein remained approximately 7.8 gm. per 100 c.c., but the albumin fraction increased from 2.6 gm. to 3.8 gm. per 100 c.c.

When transferred to the out-patient department on the thirtieth hospital day, the patient had a normal urine, no edema, and a Kahn reaction of 120 units. Three months later, after a total of 36 injections of mapharsen and six injections of bismuth, the Kahn reaction was doubtful. At that time the blood pressure was 130 mm. mercury systolic and 100 mm. diastolic. The urine was normal, with 35 per cent phenolsulfonphthalein in 15 minutes; the non-protein nitrogen was 25 mg. per 100 c.c.; the serum cholesterol, 200 mg. per 100 c.c.; and the total serum protein was 8 gm., with 4 gm. of albumin.

DISCUSSION

This patient, with no evidence of previous renal damage, abruptly developed oliguria, edema, albuminuria, cylindruria and depletion of the serum albumin. Concurrently, manifestations of secondary syphilis appeared with a Kahn reaction of high titer. The blood pressure was not elevated, and there were no eyeground changes suggesting previous vascular disease. The phenolsulfonphthalein excretion and serum non-protein nitrogen were both normal. The findings in this case satisfy the criteria set forth by Herrmann and Marr¹ for the diagnosis of acute syphilitic nephrosis.

In the cases of acute syphilitic nephrosis that have been reported, the illness has been relatively benign. The early complaints are mild and consist of malaise, headache and myalgia, common systemic symptoms in secondary syphilis. The onset of edema is abrupt and frequently accompanied by oliguria. On physical examination the striking findings are edema of the face and extremities, skin and mucosal lesions of secondary syphilis, and generalized lymph node enlargement. Evidences of chronic renal disease are invariably absent and the blood pressure and retinal vessels are normal. Albuminuria is a constant finding and the amount of protein excreted is sometimes extremely high. Moore⁵ reported a case in which 20 gm. of protein were excreted per day, and Karnoven⁶ noted an excretion of 110 gm. of protein in a day. However, 10 gm. to 20 gm. of protein per liter of urine are more commonly found. Hyaline and granular casts are present in most cases and a few white and red blood cells are usually seen. Excretion of phenolsulfonphthalein is normal and the ability of the kidneys to concentrate is not impaired. The blood non-protein nitrogen level is also normal.

The total serum proteins are lowered by depletion of the albumin fraction with resulting alteration of the albumin-globulin ratio. The increased serum globulin noted in our case is not the usual finding in nephrosis. This patient showed a negative skin and complement fixation reaction for lymphogranuloma venereum, and the cause of the hyperglobulinemia was not determined.

Serum cholesterol values are usually high, but levels as low as 150 mg. per 100 c.c. or less have been recorded. The basal metabolic rate is usually low and may show a rise coincident with antisyphilitic therapy. Attempts to find *Treponema pallidum* in the urine have been unsuccessful in these cases, although they have been reported in syphilitic patients not showing manifestations of renal disease.²

The syndrome of acute syphilitic nephrosis usually responds promptly to antisyphilitic therapy, but occasionally the condition undergoes a spontaneous

remission. In three of the 14 reported cases the nephrotic state developed after arsenical therapy had been instituted, and the question arose as to a possible nephrotoxic action of the arsenical. However, with continuation of treatment with arsenicals all evidence of nephrosis disappeared. Inasmuch as usual doses of the arsenicals have been known to cause little if any kidney injury, it is conceivable that these cases represent a Herxheimer reaction with exacerbation in *Treponema*-infected kidneys.

Various other syphilitic renal conditions have been described in the literature. These syndromes vary from a mild, transient albuminuria to severe hemorrhagic nephritis or chronic nephrosis¹ requiring months or years of antisyphilitic treatment. Most of these cases have little evidence to substantiate a syphilitic etiology, for often no thorough study was made to exclude other causes of the nephropathy. The clinical diagnosis of syphilitic renal disease is difficult and can probably never be established with absolute certainty, for there is no indisputable clinical evidence to support the rôle of syphilis in the production of a specific renal syndrome. Neither the finding of *Treponema pallidum* in the urine nor the apparent beneficial effect of antisyphilitic treatment is sufficient evidence for the diagnosis of syphilitic renal disease. The interstitial nephritis described by Rich⁷ is probably of syphilitic origin, but this condition can only be diagnosed histologically for there are no associated clinical characteristics.

The acute nephrosis associated with secondary or early syphilis is thus the only renal syndrome resulting from acquired syphilis which can be recognized clinically. The occurrence of a similar acute benign nephrosis in non-syphilitic adults is distinctly rare, if it ever occurs at all.

SUMMARY

A case of acute benign nephrosis associated with secondary syphilis is reported, and the difficulties encountered in the clinical diagnosis of syphilitic renal disease are discussed.

Addendum. After this paper was submitted for publication, two cases of acute syphilitic nephrosis treated with penicillin have been reported: TUCKER, H. A.: Penicillin treatment of acute syphilitic nephrosis and iritis, report of a case: *Am. Jr. Med. Sci.*, 1946, cxi, 718; and BARR, J. H., JR., COLE, H. N., DRIVER, J. R., LEAS, R. D., MILLER, MAX, and STRAUSS, L. S.: Acute syphilitic nephrosis successfully treated with penicillin, *Jr. Am. Med. Assoc.*, 1946, cxxxix, 741.

BIBLIOGRAPHY

1. HERRMANN, C., and MARR, W. L.: Clinical nephropathies; new case and survey of reported cases, *Am. Jr. Syph. and Neurol.*, 1935, xviv, 1-29.
2. PATTON, E. W., and CORLETTE, M. B.: Three cases of acute syphilitic nephrosis in adults, *Ann. Int. Med.*, 1941, xiv, 1975-1980.
3. KLEIN, A., and PORTER, W. B.: Nephrosis associated with early active syphilis, *South. Med. Jr.*, 1943, xxxvi, 694-697.
4. BAKER, B. M.: Relation of syphilis to nephritis, *Bull. Johns Hopkins Hosp.*, 1939, lxxv, 196-211.
5. MOORE, J. E.: The modern treatment of syphilis, 2 ed., 1941, Charles C. Thomas, Springfield, Ill.
6. KARNOVEN: *Die Nierensyphilis*, Berlin, 1901.
7. RICH, A. R.: Pathology of 19 cases of peculiar and specific form of nephritis associated with acquired syphilis, *Bull. Johns Hopkins Hosp.*, 1932, 1, 357-382.

A CASE OF AGRANULOCYTOSIS OCCURRING DURING THE COURSE OF PENICILLIN THERAPY *

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As yet, there have been no reports of the occurrence of agranulocytosis resulting from the use of penicillin. As a matter of fact, penicillin is one of the most frequently used therapeutic agents in agranulocytosis in order to prevent or to combat the associated infection. The following case, although not conclusive, suggested that on rare occasions penicillin may produce agranulocytosis.

CASE REPORT

The patient, a 54 year old white male, was admitted on October 12, 1945, to the First Surgical Division of Bellevue Hospital with the complaint of abdominal pain of five days' duration. He presented the classical symptoms and signs of acute intestinal obstruction. His previous history was non-contributory. On admission his temperature was 101.8° F., pulse 110, respirations 18, and blood pressure 120 mm. Hg systolic and 90 mm. diastolic. At this time, the white blood cell count was 13,150 with a normal differential count.

After proper preparation and with the start of penicillin (see chart for list of medication and blood counts), he was sent to the operating room and a cecostomy was performed. At this time the site of obstruction was not determined. The following day a generalized erythematous macular skin rash appeared. The dermatologist, upon consultation, stated that this rash was consistent with those appearing as a result of penicillin sensitivity. On the third day post-operatively, the temperature rose to 104.0° F. and he became psychotic. At this time the abdomen was soft and there was no distention present. A mild infection was present at the cecostomy site. The remainder of the physical examination was negative. Later in the day the white blood cell count was 2,800 with a marked reduction of the number of polymorphonuclear leukocytes (15 per cent). The following day (fourth day postoperatively), the temperature remained about 104.0° F., and another white blood cell count was 100 with no polymorphonuclear leukocytes to be seen. This count was repeated and checked by several observers with essentially the same results.

At this time, the pharynx was injected and pustules were present on the palate. Penicillin was then discontinued, a transfusion of 1000 c.c. whole blood was given, and sulfadiazine medication was started. The rash was now quite pronounced. Sixteen hours after discontinuing penicillin, the white blood cell count was 6,000 with polymorphonuclear leukocytes present in almost normal proportions. The red blood cell count was 6,500,000. That evening, the temperature dropped to 102.0° F. and the white blood cell count was then 5,200. The temperature went down to 101.0° F. on the next day and another white blood cell count was 5,000. His abdomen was soft, but a mild wound infection was still present.

On October 19, 1945, the leukocyte count was 10,700, but he became restless, vomited frequently, the blood pressure dropped and he died.

Postmortem examination revealed that there was a constricting annular carcinoma of the sigmoid colon. The cecostomy was widely patent. There was no evidence of peritonitis, but a mild necrosis and infection were present at the cecostomy site. The bone marrow revealed no abnormalities. Considerable pulmonary edema was present.

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Chart Listing Medication and White Blood Counts

Date	Time	Dosage of Penicillin	Other Medication	W.B.C.
10/12/45	9:45 p.m.	50,000 Units	Morphine sulfate, 0/01 gm. Scopolamine, 0/005 gm. Vitamin K (2 ampules)	13,150
10/12/45	11:45 p.m. (Post-op.)	50,000 Units	Prostigmine, 1/2000, 1 ampule, Q4H \times 12 Morphine sulfate, 0/01 gm., Q4H, PRN.	—
10/13/45	—	20,000 Units Q3H (This was given for 23 doses)	Vitamin C, thiamine, 5% glu- cose-saline infusion	Skin rash appeared
10/14/45	—	—	Demerol, 100 mg. Phenobarbital, 0/45 gm.	—
10/15/45	—	—	—	2,800—15% PMN'S.
10/16/45	—	Discontinued	—	100-0 PMN'S.
10/16/45	(1,000 c.c. of whole blood)			
10/17/45	16 hrs. after discontinuation of penicillin	—	Sulfadiazine, sodium bicarbonate Morphine sulfate, 0/01 gm. Sodium phenobarbital, 0/6 gm.	6,000—45% PMN'S. 5,200
10/18/45	—	—	—	5,000
10/19/45	—	—	Morphine sulfate, 0/01 gm. Digalin (2 ampules)	10,700

The anatomic diagnosis was adenocarcinoma of the sigmoid colon, recent cecostomy, mild wound infection and pulmonary edema.

In this case, in addition to the penicillin, there was other medication. This is listed on the chart. However, it does not seem likely that the other medication had any causal relation to the onset of the agranulocytosis. Some of the same medication was continued during the agranulocytosis and was given afterwards without any effect on the white blood cell count. The appearance of the skin rash, said to be typical of that seen in penicillin sensitivity, along with the rise in the white cell blood count soon after the cessation of penicillin, appears to be significant. There does not seem to have been sufficient infection present to act as a causal agent for the agranulocytosis. Although the evidence is not conclusive, it is believed this report is justified.

SUMMARY

A case is presented in which penicillin may have been responsible for the development of agranulocytosis.

HYPERTENSION AND THE KIDNEY *

By CARL A. WATTENBERG, M.D., *St. Louis, Missouri*

UNILATERAL non-nephritic kidney disease can be the cause of hypertension, and this hypertension often can be relieved by nephrectomy. This fact has been shown definitely. Many case reports have been published since the work by Goldblatt¹ and his associates, which should remove any doubt that hypertension may result from certain types of pathological unilateral renal changes. It is true that some of these cases were reported too soon following the nephrectomy, but the urologist still sees nephrectomy as a definite cure for hypertension in certain cases.

Certainly there always should be a careful urological examination of all cases of hypertension before one considers a denervation operation or medical treatment such as potassium thiocyanate. The so-called essential hypertension should have this urological study early in the disease before there can occur an arteriolar disease of the other kidney. If this change does occur then the possible cure is lost.

Flocks² recently discussed the method of study for a case of hypertension. Some of the necessary steps included a flat film to give the renal outline, a retrograde pyelogram to obtain the renal pelvis, which together gave an estimate of the renal mass. The phenolsulphonphthalein output from each kidney was determined separately following the intravenous injection. This was to give an estimate of the tubular function and, indirectly, of the blood flow through the kidney. During this same period the urea output was estimated and the urine studied for chemical or cellular abnormalities.

Braasch,³ Barker⁴ and Walters^{3,4} have shown in their recent studies that the highest incidence of hypertension occurred in patients who had a unilateral atrophic pyelonephritis. However, all cases with unilateral atrophic pyelonephritis do not have hypertension, and all cases which do have hypertension are not cured by nephrectomy of the unilateral diseased kidney.

Goldblatt¹ showed that impairment of renal circulation even when unilateral can be a cause of hypertension. Since Goldblatt's demonstration of a renal origin for hypertension, clinicians have tried to show a causal relationship between various organic lesions of the kidney and abnormal elevations of the blood pressure.

Despite the vast experimental and clinical studies on the etiologic relationship between renal change and hypertension, one cannot be sure whether or not the hypertension is of renal origin. When there is doubt, the patient should have the benefit of a nephrectomy of the unilateral diseased kidney, provided the other kidney has good function.

Cases of hypertension observed at the Mayo Clinic and reported by Braasch⁵ showed that the percentage of patients having clinical or roentgenographic evidence of unilateral "surgical" or non-nephritic renal disease was about 2.5 per cent of all the hypertensive cases studied. It was shown also in his study that less than 0.5 per cent of all hypertensive cases were suitable for nephrectomy as

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a cure for hypertension. In our study of the cases at Barnes Hospital the percentage has been less than 0.5, the best results being obtained in the younger individuals.

The following case is presented since this patient had such marked benefit following her nephrectomy for unilateral kidney disease.

CASE REPORT

Mrs. R. P. A., a white American housewife, 27 years of age, was admitted to Barnes Hospital for the second time March 30, 1943. She was complaining of severe frontal headaches, dizzy spells and nausea of three years' duration. She had had occasional ankle edema and pain in the right kidney region for several years, often nocturia, with mild burning on urination.

In 1941, on December 5, while in Barnes Hospital, she had complained of prolonged headaches, frequent colds and nasal obstruction. A submucous resection and spheno-ethmoidectomy were done for these complaints but with no benefit. Blood pressure during this visit was 150 mm. Hg systolic and 100 mm. diastolic. The urine contained one plus albumin. Catheterized urine culture had a growth of many *E. coli* organisms.

This patient, on her second admission to the hospital, was under the care of Dr. Edward Massie, an internist at Barnes Hospital, and was referred by him to me for a urological study.

The patient stated that she was well and healthy until her first pregnancy eight years before. During the last trimester she developed albuminuria and edema. Following the delivery she again was in good health. The second pregnancy six years before resulted in a spontaneous termination. Three years previously she had her third pregnancy and was getting along satisfactorily, but had a spontaneous abortion during the fifth month. Again she was feeling fine until the last trimester of her fourth pregnancy which terminated in an induced normal delivery at the eighth month, 11 months before the second admission to Barnes Hospital. During the last trimester of this fourth pregnancy, she developed a marked elevation of blood pressure with generalized edema. Following this delivery the generalized edema disappeared, but she continued to have occasional periods of edema of the ankles, hands and face. The severe left frontal headaches progressed and were accompanied by nausea and vomiting on occasion.

During the past several years the patient also had had pain in the region of the right kidney. This never was severe or colicky. It was described as a discomfort and an ache. She had periods of frequency and mild burning on urination with nocturia during the past year. There was no family history of renal or cardiac disease or migraine. The past history was essentially negative except for an appendectomy when 12 years of age, and for findings given above.

The general physical examination was negative except for the blood pressure which was 210 mm. Hg systolic and 140 mm. diastolic. The patient was well-developed and well-nourished. The eyegrounds showed each disc well outlined with no exudates or hemorrhages. The heart rate was regular with no murmurs. There was a slight enlargement of the heart to the left but no evidence of decompensation. The lungs were clear. On palpation and examination of the abdomen neither kidney could be palpated, but slight resistance and tenderness were noted in the region of the right kidney.

The blood Wassermann reaction was negative, hemoglobin 14 gm., the red cell count 4,300,000, the white cell count 7,400, and the differential count and platelets were normal. The non-protein nitrogen was 20 mg. per cent. The maximum urea clearance was 78 per cent and the standard urea clearance was 50 per cent. Fasting blood

sugar was 77 mg. per cent. Urinalysis of a catheterized urine specimen showed albumin one plus, and a centrifuged specimen stained with methylene blue revealed many rods and scattered pus cells. Basal metabolic rate was minus 1 and plus 5 per cent. The electrocardiogram was indeterminate and showed no myocardial damage.



FIG. 1. Retrograde pyelogram showing blunting and irregularity of the right calyces. The left kidney pyelogram is normal.

Cystoscopic examination revealed a generalized mild cystitis. Urine from the right kidney contained many rods as shown by culture and films stained with methylene blue. The urine from the left kidney was negative. One c.c. of phenolsulphonphthalein was given intravenously and appeared from the right kidney catheter in five minutes, and from the left kidney catheter in three minutes. The 10-minute function from the right kidney was 8 per cent and 12 per cent from the left. The plain film was normal

except that the right kidney shadow was slightly smaller than the left kidney shadow. The left pyelogram was normal, whereas the right pyelogram showed a blunting and irregularity of the calyces with some irregularity of the pelvis, as shown in figure 1.

A diagnosis of right atrophic pyelonephritis was made. The patient was discharged from the hospital for rest on April 3, 1943. She was given mandelic acid.

The patient was seen again and readmitted to Barnes Hospital June 7, 1943. The burning and frequency were much improved, but blood pressure was 220 mm. Hg systolic and 140 mm. diastolic and the headaches were severe.

A right nephrectomy was done June 9, 1943. There was a marked fibrosis surrounding the kidney and its pedicle. The outer surface of the kidney was lobulated, as seen in figure 2. The kidney was small, weighing 70 gm. The cut surface of the cortex appeared atrophic and measured about one-half centimeter in its greatest thickness (figure 3).

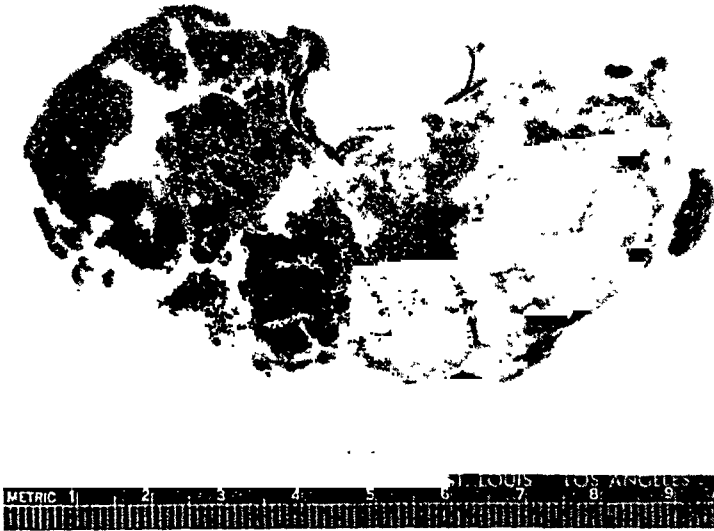


FIG. 2. Photograph of right kidney showing the outer surface scarred and lobulated. The kidney weighed 70 grams.

Microscopically, the cortex of the kidney showed interstitial fibrosis, inflammatory changes and round cell infiltration. There was an intertubular edema and fibrosis. The capillary tufts were adherent to Bowman's capsule and in several areas there was complete hyalinization, as shown in figures 4 and 5. In a few areas thick collections of inflammatory cells were present and suggested abscess formation. The small and medium-sized arteries showed intimal proliferation and some fibrosis of the media (figure 6). Section of the renal artery showed its lumen to be patent. The wall, however, was somewhat thickened.

Following the operation, there were no more attacks of dizziness nor headaches. The blood pressure gradually became lower, as seen in table 1. The patient was discharged from the hospital on her fourteenth post-operative day, with a blood pressure of 140 mm. Hg systolic and 100 mm. diastolic. She was feeling fine and stated "I feel as though I have a new lease on life." She was comfortable and had no headaches, nausea, vomiting or dizzy spells. Since her discharge from the hospital she has been seen on a few occasions and always without a complaint.

On January 10, 1944 her blood pressure was 158 mm. Hg systolic and 96 mm. diastolic. On May 8, 1944, it was 148 mm. Hg systolic and 98 mm. diastolic. Heart sounds were of normal quality and pulse was normal. Urine showed no infection when stained and contained no albumin. She has been working every day and has gained 20 pounds. On August 8, 1944 her blood pressure was 126 mm. Hg systolic and 86 mm. diastolic and she had no complaints.

On January 12, 1945 the patient's blood pressure was 120 mm. Hg systolic and 80 mm. diastolic and after activity it was 140 mm. Hg systolic and 100 mm. diastolic. The urine was negative.



FIG. 3. Photograph of inner surface of right kidney. The cortex is atrophic and measures about one-half centimeter in thickness.

A two year post-operative examination was made June 10, 1945. The patient's blood pressure was 150 mm. Hg systolic and 104 mm. diastolic after activity, and at rest it was 128 mm. Hg systolic and 88 mm. diastolic in the left arm and 132 mm. Hg systolic and 92 mm. diastolic in the right arm. The heart sounds were normal, and there was no cardiac enlargement. Her weight was 139 pounds, and she had no headaches or complaints.

A catheterized urine specimen was clear and contained no albumin or casts. A centrifuged specimen, stained with methylene blue, contained no organisms. Her blood non-protein-nitrogen was 13 mg. per cent. One c.c. of phenolsulphonphthalein given intravenously produced a 35 per cent output in 20 minutes.

The patient is considered cured of hypertension caused by unilateral renal disease.

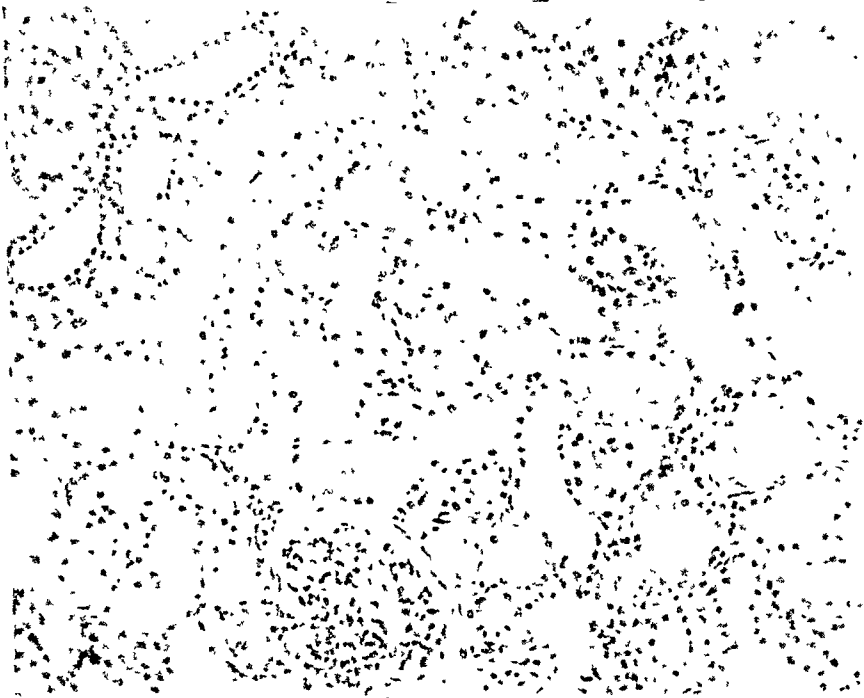


FIG. 4. Photograph of microscopic section from right kidney showing intertubular edema and fibrosis.

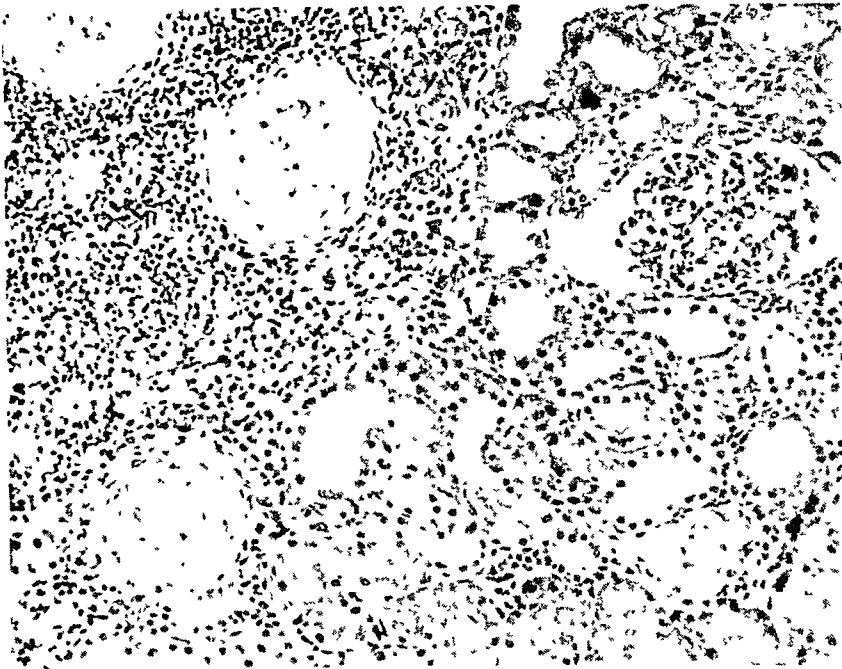


FIG. 5. Microscopic section of right kidney cortex showing interstitial fibrosis, inflammatory changes with round cell infiltration. Some of the glomeruli show complete hyalinization.

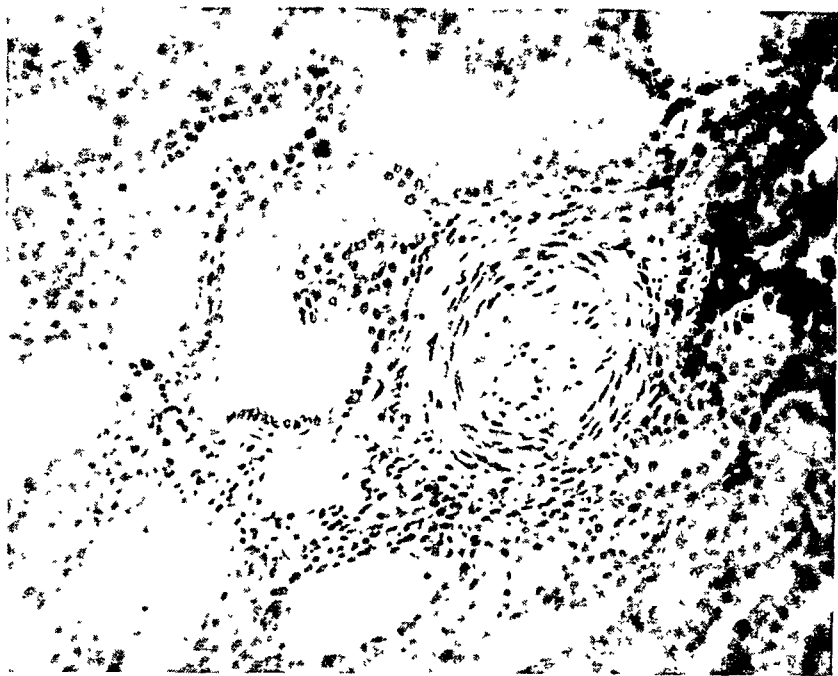


FIG. 6. Photomicrograph from right kidney showing an arteriole with endarteritis obliterans.

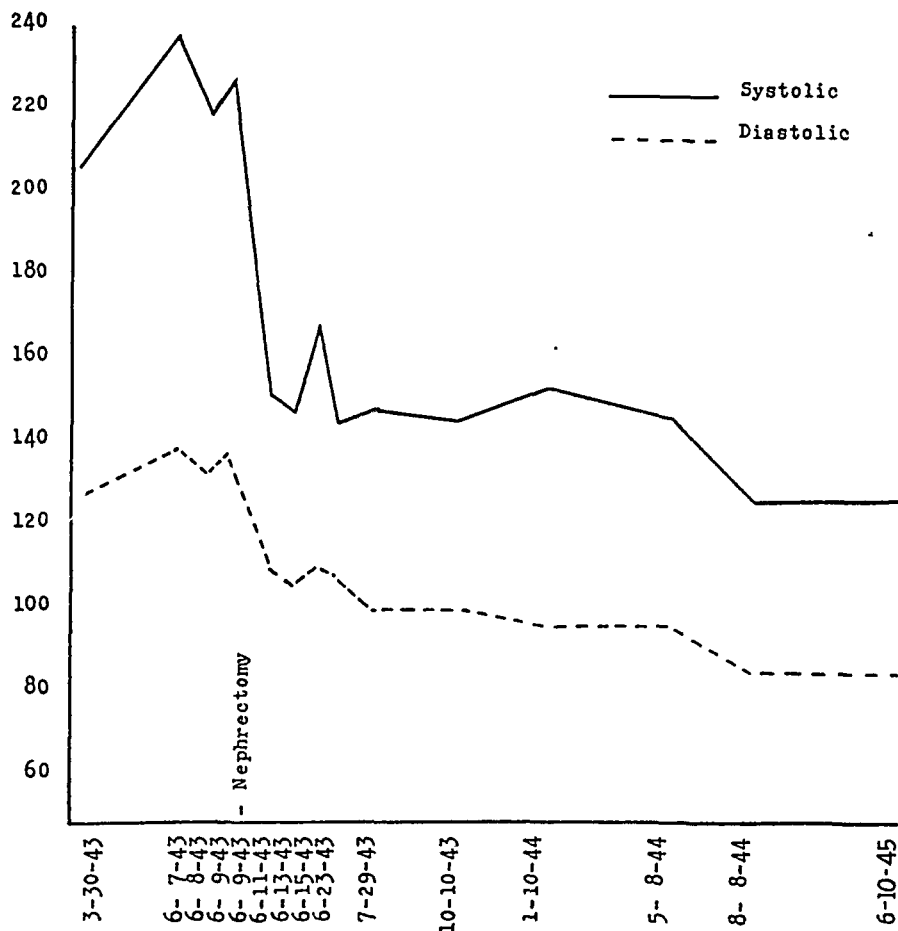


TABLE I

CONCLUSIONS

1. Unilateral renal disease, such as chronic atrophic pyelonephritis, can cause hypertension and may be cured by nephrectomy.

2. Urological examination should be carried out early in the course of hypertension if possible, before arteriolar disease of the other kidney can occur.

3. Careful urological examination should be made on all cases of hypertension before a denervation operation is performed, or before potassium thiocyanate therapy is instituted.

4. Report is made of a case which had a blood pressure of 220 mm. Hg systolic and 140 mm. diastolic, March to June 1943. Nephrectomy was done June 9, 1943. Blood pressure August 8, 1944, was 126 mm. Hg. systolic and 86 mm. diastolic. Two years post-operatively, June 10, 1945, the blood pressure was 128 mm. Hg systolic and 88 mm. diastolic. The patient had complete relief from symptoms.

Note: On Sept. 10, 1946, patient's blood pressure was 126 mm. Hg systolic and 88 mm. diastolic. Urine was negative for albumin and infection.

BIBLIOGRAPHY

1. GOLDBLATT, HARRY, LYNCH, JAMES, HANZAL, R. F., and SUMMERVILLE, W. W.: Studies on experimental hypertension. 1. The production of persistent elevation of systolic blood pressure by means of renal ischemia, Jr. Exper. Med., 1934, lix, 347-380.
2. FLOCKS, R. H.: Clinical studies on the relationship between renal disease, renal function and arterial blood pressure, Jr. Urol., 1942, xlvii, 602-613.
3. BRAASCH, W. F., WALTERS, W., and HAMMER, H. J.: Hypertension and the surgical kidney, Jr. Am. Med. Assoc., 1940, cxv, 1837.
4. BARKER, N. W., and WALTERS, W.: Hypertension and chronic atrophic pyelonephritis, Jr. Am. Med. Assoc., 1940, cxv, 912.
5. BRAASCH, W. F.: Renal disease as a factor in hypertension, Am. Jr. Surg., 1942, lvi, 209-215.

EDITORIAL

RADIOACTIVE PHOSPHORUS AS A THERAPEUTIC AGENT

RADIOACTIVE phosphorus has now been used therapeutically for several years, chiefly in the treatment of leukemia and polycythemia. Although the number of cases treated and the period of observation are still small, enough has been learned to warrant some tentative conclusions as to the value and limitations of this drug.

When ordinary phosphorus (P^{31}) is bombarded with deuterons (nuclei of heavy hydrogen) emitted at high speed by a cyclotron, an additional neutron is forced into the nucleus of some of the phosphorus atoms. This increases the mass of the atom (P^{32}), which now contains 15 protons and 17 neutrons. The number of electrons in the atom, which is identical with the number of protons present, is not changed, however, and therefore the new radioactive atom (P^{32}) is identical in its chemical reactions with the original atom (P^{31}) and can replace the latter in any inorganic or organic compounds into which phosphorus enters.

P^{32} is unstable, and one of the neutrons tends to change into a proton with simultaneous emission of an electron (beta ray), which exerts radioactivity on tissue cells or other material which it may reach. The mass of the new atom is not changed, but as it contains 16 neutrons and 16 protons and therefore 16 electrons, it is quite different chemically—it has become sulfur. The rate of this change is constant and is such that half of the radioactive phosphorus is converted into sulfur in 14.3 days (the "half-life" of P^{32}).

The radioactivity of a preparation can be measured with fair precision by means of a suitable electroscope or a Geiger counter. The unit is the millicurie, the amount of radioactivity produced by the disintegration of 37,000,000 atoms per second. No alpha or gamma rays, only beta rays are produced.

The amount of phosphorus converted into the radioactive form by the cyclotron varies with the exact conditions of the experiment but is relatively minute—ordinarily in the range of one part in one or two millions.

Phosphorus so treated can be used in making dibasic sodium phosphate or other preparations which can be administered to patients orally or intravenously. Isotonic solutions from freshly prepared material ordinarily contain about 0.2 to 0.4 millicuries per c.c.

The absorption, excretion and distribution of P^{32} in the tissues have been extensively studied by measurement of their radioactivity. Apparently the body tissues utilize P^{31} and P^{32} indifferently, the relative amount of each taken up depending solely upon the proportion of each type in the plasma and tissue fluids. Other factors being constant, therefore, the higher the concentration of P^{32} in the solution administered and the smaller the quan-

tity of P^{31} ingested in the food and from other sources, the greater will be the absolute amount of P^{32} taken up by any given tissue.

Following oral administration, about 75 per cent of the P^{32} is absorbed. Following intravenous administration, in normal individuals from 25 to 50 per cent is excreted in the urine and feces during the first four to six days. After this, the rate of excretion falls to about 1 per cent per day. In leukemia a larger proportion of the P^{32} is retained.

The relative amount of P^{32} taken up by the various tissues after the administration of a single dose varies greatly, depending upon the amount of phosphorus in the tissue and particularly upon its metabolic activity and the rate of cell multiplication. At first high concentrations are found in the bone marrow, liver, spleen and lymph nodes and somewhat lower in kidney and muscle. Later high concentrations are found in bone. Neoplastic and leukemic tissue takes up much more P^{32} than normal tissue.

The effect exerted on the tissues by P^{32} depends entirely upon the beta ray emitted when the atom disintegrates, and in general is similar to that of roentgen radiation. Although the beta ray is emitted with enough energy to penetrate about 7 mm. of tissue or fluid, its effect is largely exerted in situ and is relatively concentrated on those cells which absorb it in largest amount. Radiation applied externally must reach normal and pathological cells in equal concentration, and any specific effect it may exert on the latter must depend simply upon a greater inherent susceptibility of the pathological cells to its action. Furthermore the length of life of P^{32} is sufficient to maintain a substantial activity continuously for some days, whereas roentgen radiation can be applied only for brief intermittent periods. It would be possible, therefore, that these differences in the application of the energy might give P^{32} an advantage over roentgen radiation as a therapeutic agent.

Lawrence et al.¹ in 1939 were the first to report the treatment of chronic myelogenous leukemia (two cases) with radioactive phosphorus. Since then several reports have appeared, of which only two will be discussed. Erf, Tuttle and Lawrence² in 1941 reported a series of 46 cases of myelogenous leukemia treated with P^{32} . The eight cases of acute leukemia were not benefited. Of the 38 cases of chronic leukemia, partial remissions were obtained in 11 and complete remissions in five, whereas 21 had died. Many of these patients had previously received other types of treatment, were in advanced stages of the disease and were unfavorable subjects for any therapeutic experiment. Those who had had roentgen radiation previously responded poorly as a rule. Those who did respond favorably showed a progressive fall in the leukocyte count to normal or approximately normal values, with a reduction or even a virtual disappearance of primitive leukocytes from the peripheral blood. With this there was a rise in the erythro-

¹ LAWRENCE, J. H., SCOTT, K. G., and TUTTLE, L. W.: Studies on leukemia with the aid of radioactive phosphorus, *Internat. Clin.*, 1939, iii, 33.

² ERF, L. A., TUTTLE, L. W., and LAWRENCE, J. H.: Clinical studies with the aid of radiophosphorus. IV. The retention in blood, the excretion and the therapeutic effect of radiophosphorus on patients with leukemia, *Ann. Int. Med.*, 1941, xv, 487.

cyte count and hemoglobin, usually to normal values. There was a corresponding improvement in subjective symptoms. The spleen and liver usually diminished in size, and in a few cases they could no longer be felt. Two patients had maintained "essentially complete remissions" for nearly two years.

Reinhard et al.³ have recently reviewed the subject and reported their own results in 39 cases of myelogenous leukemia treated with P^{32} . No benefit was obtained in any of the nine acute cases. Of the 30 cases of chronic myelogenous leukemia, 12 had died and 18 were living at the time of the report. Many were unfavorable cases in an advanced stage of the disease. Eleven cases had been followed for a year or more, and all but one had had a recurrence which required further treatment during the first year. Four had been followed for more than two years and two for more than three years, all of whom had required additional treatment. Three cases had 'fairly complete' remissions maintained for a year or more without treatment. Many cases, after a more or less satisfactory remission relapsed and died in spite of further treatment. In the patients who responded favorably, the remissions were quite comparable to those described by Erf et al. The spleen was reduced in size in 23 cases and became no longer palpable in 10.

From the results thus far reported the conclusion seems warranted that P^{32} will bring about a clinical and hematological remission in chronic myelogenous leukemia which is fully equal to that obtained by roentgen radiation and with about the same certainty. It does not cure the disease. It is not yet certain whether the remissions obtained with P^{32} are longer or whether the duration of life is greater, but if there is any difference it is relatively slight. The chief advantage of P^{32} is that it does not cause radiation sickness nor the disagreeable symptoms or toxic manifestations that often accompany the administration of arsenic. In overdosage, however, either in leukemia or in other conditions, P^{32} may cause severe injury to the normal marrow cells, resulting in extreme leukopenia, thrombocytopenia or aplastic anemia.

Since there is a marked individual difference in susceptibility to this drug, great care must be taken in adjusting the dose to the needs of each patient. It has been customary to give 3 to 6 millicuries of radiation in five or six divided doses during the first two weeks and continue at less frequent intervals until a hematological remission is well under way or signs of injury to the marrow appear. Treatment is then stopped, to be resumed only when a relapse begins.

The results reported in cases of lymphatic leukemia are somewhat less favorable. Erf et al.² treated 41 cases with P^{32} . No effect was obtained in 16 acute cases (with one exception). Of 25 chronic cases, eight showed

³ REINHARD, E. H., MOORE, C. V., BIERBAUM, O. S., and MOORE, S.: Radioactive phosphorus as a therapeutic agent. A review of the literature and analysis of the results of treatment of 155 patients with various blood dyscrasias, lymphomas, and other malignant neoplastic diseases, *Jr. Lab. and Clin. Med.*, 1946, xxxi, 107.

a partial and one a complete remission. In these cases there was a substantial reduction in the total leukocyte count, but only a slight alteration in the differential count was observed. There was temporary relief of symptoms, and in most a reduction in the size of the spleen and lymph nodes.

Reinhard et al.³ reported slightly better results in a series of 45 cases of lymphatic leukemia, 15 acute and 30 chronic. At the time of the report, however, all of the acute cases and 16 of the chronic cases had died. In 20 of 24 cases with a high initial leukocyte count, the latter fell to normal levels, and in 24 of 30 cases the percentage of lymphocytes was more or less reduced. There was relatively little improvement in the anemia. Symptoms were relieved in varying degree, and there was usually some reduction in size of the spleen and lymph nodes. In some cases, however, the latter were little affected, and much greater reduction was secured by local roentgen radiation. The authors concluded that their results were no better than those obtained by roentgen radiation, the chief advantage being freedom from radiation sickness.

Reinhard et al. also obtained no benefit from the administration of P^{32} in cases of monocytic leukemia, lymphosarcoma, Hodgkin's disease, multiple myeloma and in a miscellaneous group having malignant neoplasms of various sorts. In the lymphoblastomata roentgen radiation seems to be much more effective in reducing the size of the lymph nodes than P^{32} , as the latter has heretofore been employed, even though in some cases the dose was large enough to cause serious injury to the marrow.

Cases of polycythemia vera have responded more satisfactorily to radioactive phosphorus. Lawrence⁴ in 1940 first reported the successful treatment of two cases. Since then a number of confirmatory reports have appeared, including Erf and Lawrence⁵ in 1941 (6 cases), Erf and Jones⁶ in 1943 (11 additional cases), and Hall et al.⁷ in 1945 (12 cases). More recently Reinhard et al.³ reported a series of 30 cases treated with P^{32} over a four year period. The results obtained are essentially in agreement and will be summarized as a whole.

Reinhard et al. gave 3.5 to 4 millicuries as a single intravenous injection. If the red blood cell count was over 6 million 90 days later, a second dose of 1 to 3 millicuries was given, and rarely repeated after a second 90 day interval. The total amount needed varied greatly, however, and must be adjusted for each individual patient. No more is given until a relapse occurs.

In most cases there was no appreciable change in the blood until after six

⁴ LAWRENCE, J. H.: Nuclear physics and therapy: Preliminary report on a new method of treatment of leukemia and polycythemia, *Radiology*, 1940, xxxv, 51.

⁵ ERF, L. A., and LAWRENCE, J. H.: Clinical studies with the aid of radiophosphorus. III. The absorption and distribution of radio-phosphorus in the blood of, its excretion by, and its therapeutic effect on, patients with polycythemia, *Ann. Int. Med.*, 1941, xv, 276.

⁶ ERF, L. A., and JONES, H. W.: Radio-phosphorus—an agent for the satisfactory treatment of polycythemia and its associated manifestations; a report of a case of polycythemia secondary possibly to the Banti's syndrome, *Ann. Int. Med.*, 1943, xix, 587.

⁷ HALL, B. E., WATKINS, C. H., HARGRAVES, M. M., and GIFFIN, H. Z.: Radioactive phosphorus in the treatment of polycythemia vera. Results and hematologic complications, *Am. Jr. Med. Sci.*, 1945, ccix, 712.

to eight weeks. There was then a progressive fall in red cell count, hemoglobin and hematocrit reading to normal or subnormal levels. In 11 of 30 cases the count fell below four million cells. The leukocyte and platelet counts also fell, sometimes to subnormal levels. The delayed response is explained by the assumption that P^{32} does not injure the circulating red cells but merely depresses the formation of new cells by the marrow. No fall is to be expected, therefore, until the circulating red cells wear out with age and are removed from the circulation. With the fall in red cell count there was usually substantial subjective improvement although often not complete relief of all the symptoms. The spleen became smaller in virtually all, and could no longer be felt in about two-thirds of the cases. The other objective abnormalities, particularly the red color, also largely disappeared, but hypertension if present was less affected.

The average duration of the remissions has not yet been accurately determined. In Reinhard's series, this varied from five to more than 33 months. In 17 cases the remission had lasted more than nine months; in 11, more than one year; and in five, more than two years, and many were still continuing. In only eight had a second course of treatment been required. In two reported cases^{3,7} following a remission, death occurred with the hematological features of a subacute myelogenous leukemia, an outcome fairly common under previous methods of treatment. A long period of observation will be required to compare the results of treatment with P^{32} with those obtained by other methods, particularly with spray radiation, and to determine to what extent if at all life is prolonged.

The chief drawbacks to the use of P^{32} are the cost and difficulty in obtaining the material; the risk of granulocytopenia and thrombocytopenia if the dose is excessive—which is equally a risk with roentgen radiation; and the slow initial response to treatment. In many patients with excessively high counts and severe symptoms, in whom there is a risk of thromboses, it seems advisable to carry out venesections for temporary relief during the initial period of treatment.

In conclusion, radioactive phosphorus provides a highly effective, convenient form of treatment for polycythemia vera, which is comfortable for the patient and which seems to compare favorably with the procedures commonly used. In chronic leukemia in the earlier stages of the disease it brings about remissions which are similar to those obtained by roentgen radiation, but are not significantly if at all superior. The chief advantage is freedom from radiation sickness. It does not cure the disease, and there is no proof as yet that it prolongs life. It is useless in acute leukemia. In such conditions as Hodgkin's disease, lymphosarcoma and those malignant neoplasms in which its use has been reported, it seems to be much inferior to roentgen radiation. Whenever P^{32} is used, the same precautions to avoid overdosage must be observed as are employed in giving external roentgen radiation.

REVIEWS

The Eclipse of a Mind. By ALONZO GRAVES. 722 pages; 16 × 24 cm. The Medical Journal Press, New York. 1942.

This autobiography of a newspaper man, diagnosed as manic-depressive, has been carefully edited by one of his attending physicians. The author has been hospitalized several times.

In contrast to the flood of so-called psychiatric novels, this is a work for serious study. It is probably most interesting to psychiatrists, but the sociologist, psychologist or physician concerned with human behavior, its mechanics, motivations and deviations, will find much material worth their attention.

The author is obviously a man of superior intelligence and writing ability. Although his style is often too intricate and his trend of thought at times gets confused, the book is an important and fascinating document. It not only depicts the vicissitudes and failures of a deeply troubled individual as such, but describes aptly the problematical position of a newspaper man in our culture, trying to remain independent and honest in his thinking and reporting, but hitting left and right against political and social prejudices which again and again defeat him. Some of his writing and much of his effort and attitude are reminiscent of Lincoln Steffens, the "muck raker." However, Graves lacks the balance and maturity of Steffens, not having had the benefit either of a secure family background or a thorough and broad education.

As far as the diagnosis of manic-depressive psychosis is concerned, the clinical picture is complicated by many paranoid features. In fact, the author's paranoid trends, of which he is well aware at times, are of paramount importance, in this reviewer's opinion, for a dynamic understanding of the psychotic outbreaks.

The book is well printed. It is highly recommended to serious students of human behavior and motivations.

H. W. L.

The Management of Neurosyphilis. By BERNHARD DATTNER, M.D., Jur.D., Associate Clinical Professor of Neurology, New York University Medical College, with the collaboration of EVAN W. THOMAS, M.D., Associate Professor of Medicine and Assistant Professor of Dermatology and Syphilology, New York University Medical College, and GERTRUDE WEXLER, M.D., Instructor in Dermatology and Syphilology, New York University Medical College. 398 pages; 16 × 23.5 cm. Grune and Stratton, New York. 1944. Price, \$5.50.

The authors present in a clear and logical style an adequate discussion of the complex subject of the management of neurosyphilis. The various technics involved are well presented. The text, however, was evidently prepared before the results of the experimental use of penicillin in neurosyphilis were available, so that no estimate of the possible value of this agent is included. The important subject of fever therapy is thoroughly and clearly discussed.

The authors stress the importance of changes in the spinal fluid as a guide in therapy. The technic of spinal and cisternal puncture is graphically described. The use of the Dattner type needle, which has a fine gauge, is advocated, as in the authors' experience its employment reduces the incidence of post-lumbar puncture headaches. The chapter on the examination of the spinal fluid is complete in all details.

H. M. R., Jr.

Cosmetics and Dermatitis. By LOUIS SCHWARTZ, M.D., Medical Director, U. S. Public Health Service, and SAMUEL M. PECK, M.D., Medical Director (R), U. S. Public Health Service. 189 pages with 20 illustrations. Paul B. Hoeber, Inc., New York. 1946. Price, \$4.00.

This interesting text contains information of value to both the general practitioner and the dermatologist, although naturally its greatest service will be to the latter. There are formulae of the various type cosmetic preparations on the market presented so that a case of suspected cosmetic dermatitis may be adequately studied by testing with the various ingredients as well as with the whole preparation. Because of its simplicity beauticians may find this book of value. There are brief chapters on anatomy and physiology and an adequate discussion of cutaneous allergy. The pictures are poorly reproduced and might well have been omitted, except for the frontispiece, which is an excellent illustration of dermatitis due to nail polish.

H. M. R., Jr.

BOOKS RECEIVED

Books received during August are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Medical Services by Government. By BERNHARD J. STERN, Ph.D., Columbia University. 208 pages; 21.5 × 14 cm. 1946. The Commonwealth Fund, New York. Price, \$1.50.

Medical Education and the Changing Order. By RAYMOND B. ALLEN, M.D., Ph.D. 141 pages; 21 × 14 cm. 1946. The Commonwealth Fund, New York. Price, \$1.50.

Diagnostic Examination of the Eye. By CONRAD BERENS, M.D., F.A.C.S., and JOSHUA ZUKERMAN, M.D.; F.A.C.S. 711 pages; 24 × 15.5 cm. 1946. J. B. Lippincott Company, Philadelphia. Price, \$15.00.

Disorders of the Blood. Fifth Edition. By Sir LIONEL E. H. WHITBY, C.V.O. and C. J. C. BRITTON, M.D., D.P.H. 665 pages; 25 × 16.5 cm. 1946. The Blakiston Company, Philadelphia. Price, \$10.00.

The Management of Obesity. By LOUIS PELNER, M.D. 144 pages; 22.5 × 15 cm. 1946. Personal Diet Service, New York.

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

The following gifts of publications by members are gratefully acknowledged:

Arthur Bernstein, F.A.C.P., Newark, N. J.—1 reprint.
Harold R. Carter, F.A.C.P., Denver, Colo.—2 reprints.
Earle M. Chapman, F.A.C.P., Boston, Mass.—1 reprint.
Louis J. Cheskin, (Associate), Newark, N. J.—1 reprint.
Maxwell Finland, F.A.C.P., Boston, Mass.—50 reprints.
David W. Gillick, F.A.C.P., Talihina, Okla.—2 reprints.
Samuel Gitlow, F.A.C.P., New York, N. Y.—3 reprints.
Ben H. Hollis, F.A.C.P., Louisville, Ky.—1 reprint.
Jerome G. Kaufman, F.A.C.P., Newark, N. J.—1 reprint.
Otis Gardner King, F.A.C.P., Bluefield, W. Va.—1 reprint.
Emanuel Klosk, (Associate), Newark, N. J.—1 reprint.
Victor H. Kugel, (Associate), Miami Beach, Fla.—1 reprint.
John B. Levan, F.A.C.P., Reading, Pa.—1 reprint.
Jerome S. Levy, F.A.C.P., Little Rock, Ark.—2 reprints.
Julian Love, (MC), USN, F.A.C.P., Washington, D. C.—1 reprint.
John W. Martin, F.A.C.P., Cleveland, Ohio—2 reprints.
John McEachern, F.A.C.P., Winnipeg, Man., Can.—1 reprint.
Samuel R. Mercer, (Associate), Fort Wayne, Ind.—4 reprints.
Aaron E. Parsonnet, F.A.C.P., Newark, N. J.—1 reprint.
Gustavus A. Peters, (Associate), Battle Creek, Mich.—11 reprints.
Lawrence E. Putnam, (Associate), Washington, D. C.—2 reprints.
Herbert W. Rathe, F.A.C.P., Waverly, Iowa—2 reprints.
Harold C. Robinson, F.A.C.P., Grand Rapids, Mich.—1 reprint.
Maurice J. Rotkow, (Associate), Des Moines, Iowa—1 reprint.
Howard A. Rusk, F.A.C.P., New York, N. Y.—5 reprints.
Arthur Ruskin, (Associate), Galveston, Tex.—16 reprints.
Oscar A. Sander, F.A.C.P., Milwaukee, Wis.—2 reprints.
Benjamin Saslow, F.A.C.P., Newark, N. J.—1 reprint.
Louis H. Sigler, F.A.C.P., Brooklyn, N. Y.—1 reprint.
William Stein, F.A.C.P., New Brunswick, N. J.—1 reprint.
Leon N. Sussman, (Associate), New York, N. Y.—1 reprint.
Morgan Y. Swirsky, (Associate), New Haven, Conn.—1 reprint.
Walter Howard Wilson, (Associate), Raleigh, N. C.—1 reprint.
Edwin E. Ziegler, F.A.C.P., Lancaster, Pa.—1 reprint.

PERSONNEL OF THE AMERICAN BOARD OF INTERNAL MEDICINE

Dr. William A. Werrell, Assistant Secretary-Treasurer of the American Board of Internal Medicine, has recently announced the following personnel of the Board, following elections made in May by the American College of Physicians and in July by the American Medical Association:

James J. Waring, F.A.C.P., Chairman, Denver, Colo.
William S. McCann, F.A.C.P., Vice Chairman, Rochester, N. Y.
Hugh J. Morgan, F.A.C.P., Secretary-Treasurer, Nashville, Tenn.
Marion A. Blankenhorn, F.A.C.P., Cincinnati, Ohio

LeRoy H. Briggs, San Francisco, Calif.
Alexander M. Burgess, F.A.C.P., Providence, R. I.
William B. Porter, F.A.C.P., Richmond, Va.
Burrell O. Raulston, F.A.C.P., Los Angeles, Calif.
Truman G. Schnabel, F.A.C.P., Philadelphia, Pa.
Roy W. Scott, F.A.C.P., Cleveland, Ohio
Virgil P. Sydenstricker, F.A.C.P., Augusta, Ga.
Cecil J. Watson, F.A.C.P., Minneapolis, Minn.

The Board has been increased to 12 members; it previously had nine members. Drs. Burgess, Porter and Scott are new representatives of the College.

Dr. Clarence Orion Cheney, F.A.C.P., White Plains, retired July 1 as Medical Director of the New York Hospital, Westchester Division, a position in which he served for the past ten years. Dr. Cheney previously held similar positions for fourteen years in psychiatric hospitals in New York State. He will continue in his positions as Professor of Clinical Psychiatry at the Cornell University Medical College and consulting psychiatrist to the New York, White Plains, Grasslands and other hospitals. Dr. Cheney will reside at 11 Burling Ave., White Plains, N. Y.

Dr. R. Hugh Wood, F.A.C.P., Atlanta, Ga., has accepted appointment as Dean of Emory University School of Medicine. Dr. Wood succeeds in this position Dr. Eugene A. Stead, Jr., F.A.C.P., who recently became a member of the faculty of the Duke University School of Medicine. Dr. Wood graduated from the Medical College of Virginia, Richmond, in 1921, and has held appointment at Emory University since 1921. He served in the Medical Reserve Corps of the U. S. Army for three years, retiring from it in December, 1945, with the rank of Colonel.

TRUDEAU MEDAL AWARDED

Dr. Max Pinner, F.A.C.P., Berkeley, Calif., is the recipient for 1946 of the Trudeau Medal of the National Tuberculosis Association. The citation spoke of Dr. Pinner's "curiosity and zeal to attack problems of tuberculosis and related conditions from various angles . . . recognizing that the campaign against the disease proceeds and succeeds only in proportion to its fundamental scientific soundness."

Colonel Rufus Leroy Holt, F.A.C.P., has succeeded Brig. Gen. George R. Calender, F.A.C.P., as Commandant of the Army's Professional Service School.

Secretary of War Robert F. Patterson has announced the appointment of a medical advisory committee, composed of physicians who became familiar with Army medical problems through war-time service, either as officers or civilians, to foster close relations between civilian and Army medicine, and to enable the Army to receive advice on problems of organization and policy from civilian medical leaders. The members of the committee are Dr. Edward D. Churchill, Boston, chairman; Dr. Elliott Cutler, Boston; Dr. Michael DeBakey, New Orleans; Dr. Eli Ginsberg, New York; Dr. William C. Menninger, F.A.C.P., Topeka, Kans.; Dr. Hugh J. Morgan, F.A.C.P., Nashville, Tenn.; and Dr. Maurice C. Pincoffs, F.A.C.P., Baltimore.

Dr. Arthur M. Master, F.A.C.P., New York, who served from October, 1938, to March, 1946, in the Medical Corps, U. S. Navy, retiring with the rank of Captain, has announced the resumption of the Cardiological Conferences at the Mount Sinai Hospital, New York. The Conferences, which are supervised by Dr. Master and the staff of the Hospital's Cardiology Laboratory, are held at two o'clock on the first and third Tuesday of each month in the Blumenthal Auditorium. Fellows of the College are welcome to attend.

Dr. Francis Bonneau Johnson, F.A.C.P., Charleston, S. C., has resigned from the position of Professor of Clinical Pathology in the Medical College of the State of South Carolina, to which he was appointed in 1918. A graduate of the Medical College in 1908, Dr. Johnson first received appointment to its faculty in 1908 as Assistant in Medicine.

Dr. Edward C. Reifenstein, Jr., F.A.C.P., who has engaged in research work at the Massachusetts General Hospital, Boston, for the past several years has now become Clinical Research Consultant on the staff of Ayerst, McKenna, & Harrison, Ltd. Dr. Reifenstein's office is located at 22 E. 40th St., New York, N. Y.

Dr. Stanton Tice Allison, F.A.C.P., New York, who served in the Medical Corps, U. S. Naval Reserve, from February, 1941, to July, 1946, has been commended by Admiral Halsey for outstanding service. The citation is as follows:

"For outstanding service as Director of Clinical Services on the U.S.S. BENEVOLENCE when that ship excelled in providing a screening and hospital facility for the care of the 1500 initial Allied Prisoners of War released in the Tokyo Bay area and subsequently as a hospital for the most serious prisoners released from other Japanese prison camps located in approximately two thirds of its main islands. During the three weeks that the U.S.S. BENEVOLENCE was used as the hospital ship for most seriously ill prisoners and throughout which period she cared for many hundreds of patients, only one ex-prisoner died which occurred the day after his admission. To Captain ALLISON belongs much credit for the success and excellence of the treatment administered and for the amazingly low mortality rate. He labored tirelessly and self-sacrificingly, exhibiting unusual energy and initiative. He inspired subordinates when fatigued by his indomitable spirits to renewed efforts. Captain ALLISON's conduct was at all times in keeping with the highest traditions of the United States Naval Service."

Dr. Richard Hale Young, F.A.C.P., on September 15 became Dean of the University of Utah School of Medicine and moved from Evanston, Ill., to Salt Lake City. Dr. Young graduated from the Northwestern University Medical School in 1929, and has since served on its faculty and on the staff of the Evanston Hospital. Dr. Young is a diplomate of the American Board of Internal Medicine.

Dr. Reuben A. MacBrayer, F.A.C.P., retired during July from his work with Ciba Pharmaceutical Products, Inc., of Summit, New Jersey, and is now at home at Southern Pines, North Carolina.

Dr. Thomas Van Orden Umy, F.A.C.P., formerly of Boston, has accepted the position of Director of Health at Williams College, Williamstown, Mass.

Dr. George G. Burkley, F.A.C.P., Pittsburgh, Pa., who served in the U. S. Naval Reserve from 1941 to early 1946, entered the Medical Corps of the U. S. Navy in August with rank as Captain and is now Chief of Medicine at the U. S. Naval Hospital, Charleston, S. C.

Dr. Thomas Wade Bennett, F.A.C.P., formerly of Columbia, S. C., who served during World War II in the Naval Reserve, has now entered the regular Medical Corps of the Navy with the rank of Commander and is stationed at the U. S. Naval Hospital, Philadelphia.

Col. Henry Clay Michie, F.A.C.P., retired from the Medical Corps of the U. S. Army last February, and is now residing at Alexandria, Va.

Following two years of service in the Medical Corps, U. S. Naval Reserve, from which he retired in April, 1946, with the rank of Commander, Dr. Leon Lewis, F.A.C.P., formerly of New York, has accepted appointment as Associate Professor of Industrial Health in the University of California School of Public Health. Dr. Lewis intends also to engage in private consultation practice in internal medicine, particularly as it concerns the maintenance of health of industrial workers and problems of occupational disease. Dr. Lewis will reside at 133 Ardmore Rd., Berkeley 8, Calif.

VAN METER PRIZE AWARD OFFERED

The Van Meter Prize Award of \$300, and two honorable mentions, are offered again by the American Association for the Study of Goiter for the best essays submitted concerning original work on problems related to the thyroid gland. Competing essays may cover clinical or fundamental investigations; should not exceed 3,000 words in length; and should be submitted, in English, not later than January 1, 1947, in typewritten form, double-spaced, to the Association's Corresponding Secretary, Dr. T. C. Davison, 207 Doctors Bldg., Atlanta 3, Ga. The award will be made at the annual meeting of the Association, which will occur in Atlanta, April 3-5, 1947. The essays chosen will be published in the annual Proceedings of the Association; this will not prevent their further publication in any journal selected by the authors.

Dr. Leo Victor Schneider, F.A.C.P., Glenn Dale, Md., has been awarded the Oak Leaf Cluster to the Army Commendation Ribbon for "outstanding and meritorious service" as chief tuberculosis consultant to the U. S. Military Government in Germany. Dr. Schneider served in the Medical Corps, Army of the United States, from October, 1942, to July, 1946, retiring with the rank of Lieutenant Colonel.

Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., Chairman of the Committee on Nutrition, of the Medical Society of the State of Pennsylvania, presented before a Conference on the Broad Problems of Agriculture, which occurred August 20 at Pennsylvania State College, a paper entitled "Nutrition Problems in Pennsylvania."

Col. Ernest R. Gentry, F.A.C.P., retired from the regular Army Medical Corps on September 30, 1946, and is now located in Baltimore, Md.

The University of Nebraska College of Medicine, Omaha, has announced the establishment of the Dr. Charles Frank Morsman Foundation. The Foundation, supported by a gift of \$10,000 from Dr. Charles Frank Morsman, F.A.C.P., Hot Springs, S. D., will devote its efforts to furthering the dissemination of knowledge in the field of endocrinology.

Dr. Irving Sherwood Wright, F.A.C.P., New York, who retired from the Medical Corps, Army of the United States, in February, 1946, with the rank of Colonel, has received the Army Commendation Ribbon, bestowed "for meritorious service as consultant in internal medicine, Office of the Service Command Surgeon, Headquarters, Ninth Service Command."

U. S. P. BOARD OF TRUSTEES PLANNING EARLY PUBLICATION, U. S. P. XIII

The U. S. P. Board of Trustees met recently at its headquarters in Philadelphia, 4738 Kingsessing Avenue, and laid plans for the publication of the U. S. P. XIII before the end of the current year. Plans are also being made for the development of a comprehensive program upon which to base admissions to the U. S. P. XIV. Consideration is being given to the publication of the Pharmacopoeia in Spanish as well as in English for use in Latin American countries.

Dr. David Walter Gillick, F.A.C.P., formerly of Oklahoma City, has been promoted from District Medical Director to Chief Medical Officer of the Office of Indian Affairs, Department of the Interior, and assumed his new position on July 1 at Talihina Indian Hospital, Talihina, Oklahoma.

Brigadier General George B. Foster, F.A.C.P., was retired from active duty in the U. S. Army on August 31, 1946, and has accepted an appointment as Medical Director of the Cambridge (Mass.) City Hospital.

Col. Cleon J. Gentzkow, (MC), USA, F.A.C.P., has been awarded the Legion of Merit for outstanding service as commanding officer at Deshon General Hospital, Butler, Pa., from October, 1942, to March, 1946. Dr. Gentzkow is now commanding officer of the Valley Forge General Hospital, Phoenixville, Pa.

AMERICAN ACADEMY OF OCCUPATIONAL MEDICINE

Dr. George H. Gehrmann, F.A.C.P., Wilmington, Del., has been elected President of the American Academy of Occupational Medicine. The Academy, formed at a meeting in New York in June, has as its aims prevention, diagnosis, treatment and care of occupational illness and injuries; research in pathogenesis of industrial diseases, their prevention and control; improvement in health of industrial workers. Special prerequisites have been established for membership. Drs. E. E. Evans, F.A.C.P., Penns Grove, N. J.; John H. Foulger, F.A.C.P., Wilmington, Del.; and James J. Waring, F.A.C.P., Denver, Colo., were also charter members of the Academy.

The 1947 written examination of the American Board of Internal Medicine will be held on February 17, 1947. The closing date for the acceptance of applications will be November 1, 1946.

Dr. Joseph F. Sadusk, Jr., (Associate), New Haven, Conn., has been awarded the Legion of Merit. The citation states that "Colonel Sadusk made a conspicuous contribution to the expeditious occupation of Japan . . . as preventive medicine officer for the chief surgeon in the advanced echelon of general headquarters in Japan."

Dr. Benjamin M. Bernstein, F.A.C.P., Brooklyn, New York, delivered a paper before the section of Gastro-enterology of the American Medical Association on July 3, entitled "Histamine in the Treatment of Peptic Ulcer" and also had an exhibit on the same subject.

Capt. Walter J. Pennell, F.A.C.P., has retired from the Medical Corps of the regular U. S. Navy, and on September 3, 1946, became the District Health Officer of the Massachusetts Department of Public Health. His office is in Wakefield, Mass.

Dr. Granville L. Jones, (Associate), formerly of Marlboro, New Jersey, has recently accepted appointment as superintendent of the State Hospital, Williamsburg, Va.

CORRECTION

In the August issue of this Journal, page 388, it is recorded that Dr. Nathaniel Uhr (Associate) has been retired from the Army with the rank of Colonel. Dr. Uhr retired with the rank of Lieutenant Colonel. He is now with the Veterans Administration Hospital at Topeka, Kans.

NOTE TO PHYSICIANS-ARTISTS

The \$34,000 prize contest for physicians' art work on the subject of "Courage and Devotion Beyond the Call of Duty" will be judged at the Atlantic City Centennial Session of the A.M.A. at Atlantic City June 9-13, 1947.

Art works on other subjects may also be submitted for the regular cups and medals.

For full information, write Dr. F. H. Redewill, Secretary, American Physicians Art Association, Flood Building, San Francisco, Calif., or to the sponsor, Mead Johnson & Company, Evansville 21, Ind.

Dr. J. Shirley Sweeney, F.A.C.P., has temporarily discontinued his practice in Dallas, Texas, and his teaching activities at the Baylor University College of Medicine in order to undertake, as Medical Manager, the organization of services in the Veterans Administration Hospital, Fort Logan, Colo.

RETIREMENTS FROM SERVICE

Since the last publication of this journal, the following members of the College have been reported retired or on terminal leave (to September 12, 1946 inclusive).

David I. Abramson, Cincinnati, Ohio (Major, MC, AUS)

Louis K. Alpert, Baltimore, Md. (Major, MC, AUS)

William F. Ashe, Jr., Cincinnati, Ohio (Major, MC, AUS)
Oscar Auerbach, Staten Island, N. Y. (Lt., MC, USNR)
Russell L. Baker, White Salmon, Wash. (Major, MC, AUS)
Ralph G. Ball, Manhattan, Kans. (Col., MC, AUS)
William E. G. Bayley, La Crosse, Wis. (Major, MC, AUS)
Charles A. Breck, Wallingford, Conn. (Major, MC, AUS)
Martin G. Carter, Los Angeles, Calif. (Capt., MC, USNR)
Thomas E. Clark, Columbus, Ohio (Lt., MC, USNR)
James P. Crawford, Del Monte, Calif. (Col., MC, USA)
Robert W. Currie, Billings, Mont. (Major, MC, AUS)
James H. Danglade, Kansas City, Mo. (Comdr., MC, USNR)
Marion T. Davidson, Birmingham, Ala. (Major, MC, AUS)
William C. Dine, Jr., Amarillo, Tex. (Capt., MC, AUS)
Kenneth L. Druet, Salina, Kans. (Lt. Col., MC, AUS)
Daniel B. Faust, Ozark, Ala. (Col., MC, USA)
M. Herbert Fineberg, Boston, Mass. (Col., MC, AUS)
George B. Foster, Jr., Philadelphia, Pa. (Brig. Gen., MC, USA)
Richard France, Baltimore, Md. (Capt., MC, USNR)
Elmer S. Gais, New York, N. Y. (Col., MC, AUS)
Frederick Goldman, Cincinnati, Ohio (Lt., MC, USNR)
Martin G. Goldner, Chicago, Ill. (Capt., MC, AUS)
Seymour J. Gray, Chicago, Ill. (Lt. Comdr., MC, USNR)
George F. Harsh, San Diego, Calif. (Comdr., MC, USNR)
Robert A. Hollands, Pasadena, Calif. (Major, MC, AUS)
John A. Hookey, Sr., Detroit, Mich. (Major, MC, AUS)
Roger H. Keane, Portland, Ore. (Lt. Comdr., MC, USNR)
William E. Kendall, Dwight, Ill. (Col., MC, AUS)
Byrl R. Kirklin, Rochester, Minn. (Col., MC, AUS)
Milton L. Kramer, New York, N. Y. (Lt. Col., MC, AUS)
Victor H. Kugel, New York, N. Y. (Major, MC, AUS)
Howard F. Lawrence, Warren, Pa. (Capt., MC, USN)
John A. Layne, Great Falls, Mont. (Major, MC, AUS)
Byrd S. Leavell, Charlottesville, Va. (Major, MC, AUS)
Isaiah E. Libin, New York, N. Y. (Capt., MC, AUS)
Charles F. Lowry, Kansas City, Mo. (Lt. Col., MC, AUS)
Arthur A. Marlow, La Jolla, Calif. (Col., MC, AUS)
John K. Martin, Seattle, Wash. (Col., MC, AUS)
Alexander McCausland, Blacksburg, Va. (Lt., MC, USNR)
Alphonse McMahon, St. Louis, Mo. (Commodore, MC, USNR)
Perry J. Melnick, Chicago, Ill. (Lt. Col., MC, AUS)
Joseph A. Mendelson, Washington, D. C. (Lt. Col., MC, USA)
M. Hill Metz, Dallas, Tex. (Lt. Comdr., USPHS (R))
Samuel Myerson, New York, N. Y. (Capt., MC, AUS)
Don E. Nolan, Dayton, Ohio (Lt. Col., MC, AUS)
Robert B. Nye, Philadelphia, Pa. (Col., MC, AUS)
Kenneth A. Owen, Akron, Ohio (Major, MC, AUS)
Andrew J. Parker, Pittsburgh, Pa. (Major, MC, AUS)
Walter J. Pennell, Auburn, Maine (Capt., MC, USN)
George P. Perakos, New Britain, Conn. (1st Lt., MC, AUS)

Gilberto S. Pesquera, Mount McGregor, N. Y. (Major, MC, AUS)
 Theodore J. Pfeffer, Racine, Wis. (Lt. Col., MC, AUS)
 Arthur H. Reynolds, New York, N. Y. (Capt., MC, AUS)
 Paul H. Revercomb, Charleston, W. Va. (Lt. Col., MC, AUS)
 Monroe J. Romansky, Rochester, N. Y. (Major, MC, AUS)
 Leon Rosove, Santa Monica, Calif. (Comdr., MC, USNR)
 John J. Rupp, Santa Barbara, Calif. (Capt., MC, USNR)
 Henry I. Russek, Brooklyn, N. Y. (Lt. Comdr., USPHS (R))
 Earl Saxe, Topeka, Kans. (Lt. Col., MC, AUS)
 Nathan Schaffer, East Orange, N. J. (Lt. Col., MC, AUS)
 Harry T. A. Seneca, New York, N. Y. (Lt., MC, AUS)
 Emil M. Shebesta, Detroit, Mich. (Major, MC, AUS)
 Emory L. Shiflett, Louisville, Ky. (Lt. Col., MC, AUS)
 Charles L. Spurr, Chicago, Ill. (Lt., MC, USNR)
 Robert E. Stone, Chapel Hill, N. C. (Capt., MC, AUS)
 Morgan Y. Swirsky, New Haven, Conn. (Capt., MC, AUS)
 Ernest M. Tapp, Walla Walla, Wash. (Lt. Col., MC, AUS)
 Morris C. Thomas, Indianapolis, Ind. (Col., MC, AUS)
 T. Noxon Toomey, Springfield, Ill. (Major, MC, AUS)
 Joseph Weinstein, Brooklyn, N. Y. (Lt. Col., MC, AUS)
 Francis R. Whitehouse, Rochester, Minn. (Major, MC, AUS)
 Udo J. Wile, Ann Arbor, Mich. (Col., USPHS)
 John W. Williams, Cambridge, Mass. (Comdr., USPHS (R))
 Ellis W. Young, Pittsburgh, Pa. (Capt., MC, AUS)
 Solomon L. Zimmerman, Columbia, S. C. (Lt. Col., MC, AUS)

BOARD OF REGENTS MEET IN PHILADELPHIA OCTOBER 19-20

The Board of Regents of the College held its annual autumn meeting in Philadelphia, October 19-20, and the proceedings will be published in these columns as soon as possible. It is at the autumn meeting that much of the main business of the College is transacted, such as adoption of budget, approval of programs of postgraduate courses, designation of available Fellowships to be awarded election of new Associates and Fellows, etc. It is also anticipated that growing out of the proceedings of this meeting will be an official statement clarifying in greater detail the requirements and criteria of membership.

OMISSION

In the account of the Forty-Seventh Meeting of the American Gastroenterological Association (College News Notes, August, 1946), the list of participants failed to include Dr. Manfred Kraemer, F.A.C.P., Newark, N. J. Dr. Kraemer presented a paper at the meeting, entitled, "Malnutrition in American Prisoners."

WESTERN NEW YORK MEMBERS HOLD REGIONAL MEETING

Under the Governorship of Dr. Edward C. Reifenshtein, Sr., a Regional Meeting of the American College of Physicians was held for members in Western New York, at Syracuse, October 16, 1946. The scientific program was as follows:

1. The Treatment of Empyema of the Pleural Cavity by Penicillin Used Intrapleurally.

Paul C. Clark, M.D., F.A.C.P., Syracuse.

2. Hiatus Hernia.

Henry H. Haft, M.D., F.A.C.P., Syracuse.

3. Certain Clinical and Pathological Manifestations of Periarthritis Nodosa.

J. Winthrop Pennock, M.D., F.A.C.P., Syracuse.

4. Clinical-Pathological Studies of Rheumatic Carditis.

George H. Reifenstein, M.D., Syracuse.

5. The Renal Mechanisms Involved in Stabilizing the Alkali Reserves of the Body.

Robert F. Pitts, M.D., New York, N. Y.

6. The Scope of Modern Psychiatry.

John Romano, M.D., Rochester.

7. Visual Manifestations of Digitalis Poisoning.

David F. Gillette, M.D., Syracuse.

8. Clinical-Pathological Conference.

J. Howard Ferguson, Syracuse; Drs. William S. McCann, F.A.C.P., Rochester, and Nelson G. Russell, Sr., F.A.C.P., Buffalo, Discussors.

An evening reception was followed by a dinner at the Onondaga Golf and Country Club, at which Dr. Wardner D. Ayer, F.A.C.P., Syracuse, addressed the group on "Certain Phases of the History of Medicine, Based on the Wolf Portraits, College of Medicine at Syracuse University."

Dr. Richard D. Kepner, F.A.C.P., Honolulu, T. H., has been appointed consultant to the Secretary of War.

PLANS UNDER WAY FOR TWENTY-EIGHTH ANNUAL SESSION

The plans for the Twenty-Eighth Annual Session of the American College of Physicians, which will be held in Chicago, April 28-May 2, 1947, are now well under way. Dr. LeRoy H. Sloan, General Chairman, is now actively engaged in completing his Roster of Committees, which will include not only the Executive Committee to formulate the planning of the entire program of clinics and panel discussions, but also committees for the individual hospitals which will participate. Dr. Sloan and the members of the committee are most enthusiastic workers. They are determined that this shall be a most rewarding and memorable meeting.

In anticipation of the largest attendance that the College has ever had at an Annual Session, the Palmer House has been selected as headquarters, and arrangements have been made with numerous other hotels in order to reserve the maximum number of rooms that can be procured. A Committee of Physicians, well acquainted with the College Membership, will be named by Dr. Sloan to work in conjunction with the Chicago Convention Bureau on housing arrangements. This Committee will hold weekly conferences in order to make the best possible assignments of rooms to applicants.

Dr. David P. Barr, President, is now making preliminary arrangements concerning subjects and speakers for the Morning Lectures and General Sessions.

Mr. E. R. Loveland, Executive Secretary, is engaged in laying out the floor plans for the Technical Exhibits, in which interest has been shown by a considerable number of outstanding pharmaceutical firms and supply houses, and reports that the business arrangements for the meeting are now well along.

Major General Shelley U. Marietta, (MC), USA, Ret'd., F.A.C.P., Washington, D. C., was elected to the position of President-Elect, and Dr. Louis Mark, F.A.C.P.,

Columbus, Ohio, to that of Second Vice-President, of the American College of Chest Physicians, at the annual meeting of the College which took place at San Francisco in June.

The employes of the San Francisco Department of Public Health recently presented Dr. J. C. Geiger, F.A.C.P., with a beautiful scroll on the occasion of his fifteenth anniversary as Director of Public Health of the City and County of San Francisco. The citation refers to Dr. Geiger's "untiring devotion to duty . . . leadership which has brought international attention to the efficiency and progressiveness of the San Francisco Department of Public Health . . . unusual and continuous personal interest in the employes."

CAPTAIN TURVILLE PRESENTS BOOK, U. S. NAVAL MOBILE HOSPITAL NUMBER EIGHT,
TO THE COLLEGE

Captain William H. H. Turville, (MC), USN, F.A.C.P., has presented to the College a copy of the book delineating the development and history of the U. S. Naval Mobile Hospital Number Eight from the time of its commission, on August 12, 1942, until the date of his detachment as Commanding Officer of the hospital, May 17, 1944. The hospital was located on Guadalcanal and the book contains many interesting illustrations and is a most interesting narrative of the organization, building and administration of one of the most important of these novel hospitals. It forms a valuable addition to the College Archives because of the many intimate reports about not only Captain Turville but many other Fellows of the College who were connected with the Hospital.

Dr. Donald T. Chamberlin, F.A.C.P., has now returned to Boston, is limiting his practice to diseases of the digestive system, and has a teaching connection with Harvard University and the Boston City Hospital. He is located at 422 Beacon St.

Dr. Eugene P. Campbell, F.A.C.P., is Chief of the Field Party of the Brazil Division of Health and Sanitation of the Institute of Inter-American Affairs, and is at present stationed at Rio de Janeiro, Brazil. The Cooperative Public Health Program of the Governments of the United States of America and Brazil presented a series of 12 papers before the First Inter-American Medical Congress.

Announcement has been made of the formation of a new committee of the National Research Council which will give advice to the Veterans Administration on medical problems. Dr. O. H. P. Pepper, F.A.C.P., Philadelphia, will act as Chairman of the Committee; its members include the following Fellows of the College: Dr. Hugh J. Morgan, Nashville, Tenn.; Dr. Francis J. Braceland, Rochester, Minn.; Dr. William C. Menninger, Topeka, Kans.; Dr. C. P. Rhoads, New York; and Dr. J. Roscoe Miller, Chicago.

The 98th Annual Meeting of the Medical Society of Virginia was held October 14-16, 1946, at the Cavalier Hotel, Virginia Beach, with Dr. A. Brownley Hodges, F.A.C.P., Norfolk, as Chairman of the Committee on Arrangements. The program of the sessions disclosed the following members of the College to be participants. Dr. Walter B. Martin, F.A.C.P., Norfolk, delivered an address at the Monday evening

session and a paper on "Laboratory and Diagnostic Methods of Interest to the General Practitioner" on Wednesday. Drs. Charles M. Caravati, F.A.C.P., and James M. MacMillan, (Associate), Richmond, presented a paper, entitled, "Gastroscopy: An Aid in the Diagnosis of Occult Hematemesis." Dr. Oscar Swineford, Jr., F.A.C.P., University, was co-author of a paper, "The Coseasonal Treatment of Hay Fever," which was discussed by Dr. J. Warrick Thomas, F.A.C.P., Richmond. Dr. Frank H. Redwood, F.A.C.P., Norfolk, discussed the "Present Status of Shock Therapy," which was presented by Dr. R. Finley Gayle, Jr., F.A.C.P., Richmond, co-author. Dr. Paul D. Camp, F.A.C.P., Richmond, was co-author of a report on the subject, "Severe and Fatal Rheumatic Fever with Pancarditis in Virginia." Dr. Julian R. Beckwith, F.A.C.P., Clifton Forge, spoke on "Hypertensive Vascular Disease: Its Evaluation and Management." Participating in a symposium on general practice, Dr. Joseph R. Blalock, F.A.C.P., Marion, presented "Neuropsychiatry as It Relates to the General Practitioner." Dr. George F. Lull, F.A.C.P., Chicago, delivered an address at the Tuesday dinner session.

Dr. Harry W. Shuman, F.A.C.P., Rock Island, Ill., spoke before the Iowa-Illinois Central District Medical Association at Moline, Ill., September 12, 1946, on the subject, "Cardiac and Circulatory Changes in Hyperthyroidism."

Dr. Hobart A. Reimann, F.A.C.P., Professor of Medicine at Jefferson Medical College of Philadelphia, and Dr. William D. Stroud, F.A.C.P., Professor of Cardiology in the University of Pennsylvania Graduate School of Medicine, have been named as two of the 20 members of the National Medical and Scientific Advisory Council of the National Arthritis Research Foundation. This foundation has been organized recently to study the causes, cure and prevention of arthritis and related rheumatic diseases. The American College of Physicians appropriated \$1,000 as a donation to the work. A special research center will be established in Hot Springs National Park, Ark.

At a recent meeting to support the Foundation's drive for funds, Dr. Thomas Parran, F.A.C.P., Surgeon General of the U. S. Public Health Service, estimated the cost of medical care of the 3,000,000 persons in the United States who suffer from arthritis and other rheumatic diseases to be of the order of \$100,000,000 a year.

DR. KERN BECOMES PROFESSOR OF MEDICINE AT TEMPLE

Dr. Richard A. Kern, F.A.C.P., Philadelphia, has been appointed to the positions of Professor and Head of the Department of Medicine in the Temple University School of Medicine, and Medical Director of the Temple University Hospital. Dr. Kern succeeds Dr. Charles L. Brown, who recently became Dean of the Hahnemann Medical College and Hospital of Philadelphia.

Dr. Kern is a graduate of the University of Pennsylvania School of Medicine, class of 1914, and has since had a distinguished career in the faculty of that school as well as in the University's Graduate School of Medicine, in each of which he held a Professorship of Clinical Medicine. Dr. Kern served in the Navy Medical Corps in both wars; during World War II, he served as the head of Naval Medical Reserve Specialists Unit No. 9, which staffed the U.S.S. Solace, the only hospital ship in the Pacific during the early part of the war. In 1943 Dr. Kern was assigned to Admiral Halsey's staff in the South Pacific, as Medical Consultant, and, from 1944 to

the end of 1945, he served as Chief of Medicine and Rehabilitation Officer at the U. S. Naval Hospital, Philadelphia, retiring from the Navy with the rank of Commadore. Dr. Kern is presently serving as consultant to the Veterans Administration and as chief of its section for general medicine.

Dr. Anthony Bassler, F.A.C.P., New York, has been elected President of the National Gastroenterological Association, and Drs. Clarence J. Tidmarsh, F.A.C.P., Montreal, and Harry M. Eberhard, (Associate), Philadelphia, have been elected Vice Presidents.

Dr. G. Nelson Furbeck, (Associate), of Mexico City, was released from active duty in the Army last January, and spent the first semester of this year at Tulane University of Louisiana, taking a postgraduate course in tropical medicine. He has now resumed practice at his old location, Gante 1, Mexico, D. F.

While on active duty in the Army, during June, 1945, Dr. Furbeck was awarded the Bronze Star Medal, "for meritorious service in connection with military operations against the enemy at Okinawa Shima, Nansei Shoto, during April, 1945. During an early dawn shelling of the battalion and station by the enemy, Captain Furbeck, the battalion surgeon, was painfully wounded. Within a short period of time the aid station was filled with casualties evacuated from front line units. Disregarding his own wounds, he treated the wounded and arranged for their evacuation, although to do so he was forced to fight down successive waves of nausea caused by his own wounds. He remained on duty all day, steadfastly refusing to be evacuated until relief arrived and another surgeon could take over his duties. His unselfish devotion to duty and to the needs of the wounded was an inspiration to all who saw him in action and was accomplished in the highest traditions of the country he serves." On November 9, 1945, Dr. Furbeck received further official commendation from Col. W. S. Winn, Commanding the Headquarters of the 105th infantry.

Dr. Robin C. Buerki, F.A.C.P., Dean of the Graduate School of Medicine, and Director of Hospitals, of the University of Pennsylvania, Philadelphia, was one of three physicians who received appointment to the Federal Hospital Council. The Surgeon General of the U. S. Public Health Service, Dr. Thomas Parran, F.A.C.P., is *ex officio* Chairman of the Council which will have the responsibility for approving the general regulations for the program of hospital surveys and construction authorized by the Hill-Burton bill.

Dr. Robert J. Mearin, (Associate), New York, was recently commended by Admiral H. K. Hewitt, USN, for his activities as senior medical officer, Advanced Amphibious Training Base, Bizerte, Tunisia, October, 1944, to May, 1945. The citation mentions the following outstanding services: "exceptional professional and administrative ability and energy in supervising medical activities . . . prompt analysis of the problems involved and the initiative which you displayed in instituting control measures completely protected the United States Navy personnel of the . . . Base . . . from this dread disease (bubonic plague) . . . sound judgment and outstanding devotion to duty." Dr. Mearin retired from the Medical Corps, USNR, in May, 1946, with the rank of Lieutenant Commander.

Dr. Samuel A. Levine, F.A.C.P., Boston, delivered the Walter Wile Hamburger Memorial Lecture of the Institute of Medicine of Chicago, October 8, 1946. Dr. Levine's subject was "Treatment of Congestive Heart Failure."

The 96th meeting of the Kentucky State Medical Association occurred September 30-October 3, 1946, at Paducah. The program of speakers included the following:

Dr. Rankin C. Blount, F.A.C.P., Lexington, "Pathogenesis and Treatment of Essential Hypertension."

Dr. Thomas M. Marks, F.A.C.P., Lexington, "What Benefit if Any Does Prostigmine Offer to Cerebral Palsy?"

Dr. William K. Keller, F.A.C.P., Louisville, "Psychiatry for the General Practitioner."

Dr. Samuel A. Overstreet, F.A.C.P., Louisville, "More Stately Mansions."

Dr. Maurice A. Shillington, F.A.C.P., Glendive, has become President of the Montana State Medical Association.

Dr. J. Franklin Waddill, F.A.C.P., Norfolk, Va., has been awarded the Army Commendation Ribbon. The citation states that the award was made for "outstanding and meritorious service as Chief of the Medical Service, Station Hospital, Fort Eustis, Virginia, from September 1942 to June 1944. Colonel (then Lieutenant Colonel) Waddill's administration of the medical service, his teaching program and especially the establishment of a heat disease program helped to maintain a high standard of medical attainment. His persistent adherence to the principles involved in his line of endeavor prevailed to the end that its value to the military service is fully recognized. His efforts have brought great credit to himself, have been of inestimable value to the command and have contributed much to the advancement of medicine in the field of heat disease, meningitis, cardiovascular disease and pneumonia."

Drs. George S. Lull, F.A.C.P., Chicago, and Frank B. Queen, F.A.C.P., Portland, were listed as speakers in the program of the 72nd meeting of the Oregon State Medical Society, which took place at Gearhart, September 26-28, 1946. Dr. Lull's topic was "Activities of Organized Medicine." Dr. Queen discussed "Some Current Problems in Cancer."

The following Fellows of the College participated as speakers at the 105th meeting of the State Medical Society of Wisconsin, Milwaukee, October 7-9, 1946:

Dr. M. Herbert Barker, Chicago, "Infectious Hepatitis."

Dr. Paul D. White, Boston, "The Most Important Therapeutic Measures in the Treatment of Hypertensive Heart Disease."

Dr. Wesley W. Spink, Minneapolis, "Antibiotics."

Dr. J. Arthur Myers, Minneapolis, "The Physician and Tuberculosis."

Dr. Carl V. Moore, St. Louis, "Use of Folic Acid in Treatment of Macrocytic Anemias."

The American Academy of Allergy will hold its annual convention at Hotel Pennsylvania, New York City, November 25 to 27, inclusive. All physicians interested in allergic problems are cordially invited to attend the sessions as guests of the Academy without payment of registration fee. The program has been arranged to cover a wide variety of conditions where allergic factors may be important. Papers will be presented dealing with the latest methods of diagnosis and treatment as well as the results of investigation and research. Advance copies of the program may be obtained by writing to the Chairman on Arrangements, Dr. Horace S. Baldwin, 136 East 64th Street, New York City, prior to November 10.

THE A. C. P. AUTUMN PROGRAM OF POSTGRADUATE COURSES

Four of the College courses on the Autumn, 1946 schedule have now been concluded, namely, No. 1, Internal Medicine, at the University of Pittsburgh; No. 2, Psychosomatic Medicine, at the University of Colorado; No. 3, Internal Medicine, at the University of Oregon; No. 4, Clinical Neurology, at the Jefferson Medical College, Philadelphia.

Courses Nos. 1, 2 and 4 were all oversubscribed. Course No. 3, Internal Medicine, at the University of Oregon, one of the fine courses on the College program, had a relatively small registration because of the lateness in publishing the detailed outline, due to difficulties in the director's office. It is regretted that so fine a course could not have been more widely publicized and taken advantage of by a larger number of College members and other interested physicians.

Course No. 1 deserves special comment. It was given under the direction of Dr. R. R. Snowden, F.A.C.P., during the first two weeks of September. Dr. Snowden was assisted by physicians from virtually every hospital in the Pittsburgh area. A Regional Meeting of the College for Western Pennsylvania was held on September 11, and the program made a part of the course. The Regional Meeting was concluded by a dinner in the evening at the Pittsburgh Athletic Association and was addressed by Dr. George Morris Piersol, Secretary General, and by Dr. Edward L. Bortz, Chairman of the College Committee on Postgraduate Courses, both of Philadelphia. All members of the class and of the faculty were invited as guests to the Regional Meeting. This was the first time the College has given a course in Pittsburgh. A report from the Director indicates his satisfaction with the interest shown by the attending class. The Executive Officers of the College have received several spontaneous letters from physicians who took this course, expressing their appreciation in the highest terms.

The matriculation fees were used to defray local expenses, entertainment, traveling expenses of guest speakers, and for the purchase of a microfilm projector and microfilmed books which were presented to the Presbyterian Hospital where much of the course was conducted. The Presbyterian Hospital will use this apparatus and books for patients who cannot otherwise read, the films being projected on the ceiling above the patient's bed. The gift was made in appreciation for the great efforts put forth by the hospital in making this Postgraduate Course a success.

Courses Yet to Be Concluded

No. 5—Clinical Medicine from the Hematologic Viewpoint, Ohio State University College of Medicine, Columbus, Ohio; Dr. Charles A. Doan, F.A.C.P., Director; October 21–26, 1946.

This course has been registered to its full capacity, 75.

No. 6—Internal Medicine, Gallinger Municipal Hospital, Washington, D. C.; Dr. Wallace M. Yater, F.A.C.P., Director; October 21–November 1, 1946.

This course has a large registration but is not filled to the maximum capacity of 100.

No. 7—Allergy, Roosevelt Hospital, New York, N. Y.; Dr. Robert A. Cooke, F.A.C.P., Director; November 4–9, 1946.

This course has an adequate registration but can still accommodate a few additional registrants.

No. 8—Recent Advances in the Diagnosis and Treatment of Cardiovascular Disease, Massachusetts General Hospital, Boston, Mass.; Dr. Paul D. White, F.A.C.P., Director; November 4–9, 1946.

Although the detailed outline of this course was not published in the Postgraduate Bulletin due to the absence of the Director in Europe, the

course has been oversubscribed by an exceedingly large number. Many of those who cannot be accommodated this year have requested that their names be placed on the waiting list for the next time it is repeated.

- No. 9—Gastro-enterology, University of Chicago School of Medicine, Chicago, Ill.; Dr. Walter Lincoln Palmer, F.A.C.P., Director; November 11-15, 1946.

This course has been registered to its capacity of 85.

- No. 10—Selected Problems in Internal Medicine, Western Reserve University, Cleveland, Ohio; Dr. Joseph M. Hayman, Jr., F.A.C.P., Director; November 18-23, 1946.

Although this course is new on the College program, it has a very adequate registration. There may be a limited number of vacancies available.

- No. 11—Internal Medicine, Royal Victoria Hospital, Montreal, Que.; Dr. J. C. Meakins, F.A.C.P., Director; November 25-December 6, 1946.

It is anticipated that this course will be filled to the capacity of 60, although a few vacancies exist.

- No. 12—Bacterial Chemotherapy, Washington University School of Medicine, St. Louis, Mo.; Dr. W. Barry Wood, Jr., F.A.C.P., Director; December 2-7, 1946.

This a limited course, restricted to 20. Twelve have registered at the time of preparation of this report.

- No. 13—Cardiology, University of Michigan Medical School, Ann Arbor, Mich.; Dr. Frank N. Wilson, F.A.C.P., Director; December 2-7, 1946.

This course has been greatly oversubscribed but it is hoped that the Director will repeat the course during 1947 and thus accommodate many members who are on the waiting list.

The Spring, 1947 Schedule

In the next issue of this journal we hope to be ready to announce the complete outline of courses to be offered by the College during the winter and spring of 1947. Tentatively under consideration are the following:

ARTHRITIS AND ALLIED CONDITIONS

(Probably at the Mayo Clinic)

CARDIOVASCULAR DISEASE, Dr. Bruce Logue, F.A.C.P., Director

Emory University School of Medicine, Atlanta, Ga., during March

CARDIOVASCULAR DISEASE, Dr. J. Roscoe Miller, F.A.C.P., Director

Northwestern University, Chicago, Ill.; April 21-26, 1947

CARDIOVASCULAR DISEASE, Dr. Thomas M. McMillan, F.A.C.P., Director

Philadelphia General Hospital, Philadelphia, Pa.

CARDIOVASCULAR DISEASE, Dr. Arthur M. Master, F.A.C.P., Director

Mt. Sinai Hospital, New York City

DISEASES OF THE CHEST, Dr. J. Burns Amberson, F.A.C.P., Director

Bellevue Hospital, New York City

GASTRO-ENTEROLOGY, Dr. Henry L. Bockus, F.A.C.P., Director

Graduate Hospital, Philadelphia, Pa.

GENERAL MEDICINE, Dr. James E. Paullin, F.A.C.P., Director

Emory University, Atlanta, Ga.

INTERNAL MEDICINE, WITH EMPHASIS UPON NUTRITION AND METABOLISM, Dr.

M. A. Blankenhorn, F.A.C.P., Director

Cincinnati General Hospital, Cincinnati, Ohio

INTERNAL MEDICINE

Massachusetts General Hospital, Boston, Mass.

NEUROPSYCHIATRY, Dr. Hans Reese, F.A.C.P., Director

University of Wisconsin, Madison, Wis.; or Dr. Roland P. Mackay, F.A.C.P.,
Director

University of Illinois, Chicago, Ill.; or Dr. Edward A. Strecker, F.A.C.P.,
Director

Institute of the Pennsylvania Hospital, Philadelphia, Pa.

MECHANICS OF DISEASE, Dr. George W. Thorn, F.A.C.P., Director

Peter Bent Brigham Hospital, Boston, Mass.

PERIPHERAL VASCULAR DISEASE, Dr. E. V. Allen, F.A.C.P., Director

Mayo Foundation, Rochester, Minn.

PHYSICAL MEDICINE, Dr. George Morris Piersol, F.A.C.P., Director

University of Pennsylvania, Philadelphia, Pa.

PSYCHOSOMATIC MEDICINE, Dr. Franklin G. Ebaugh, F.A.C.P., Director

University of Colorado, Denver, Colo.

TISSUE GROWTH AND TUMORS, Dr. Stanley Reimann, F.A.C.P., and Dr. E. L.
Bortz, F.A.C.P., Directors

Lankenau Hospital, Philadelphia, Pa.

The Advisory Committee on Postgraduate Courses will also consider additional courses in Internal Medicine and other allied specialties. The above suggestions are purely tentative. Watch these columns for developments.

OBITUARIES

DR. EDWARD GODFREY HUBER

Dr. Edward Godfrey Huber, F.A.C.P., Waban, Mass., Professor of Public Health Practice at Harvard University, died July 23, 1946, aged 64 years. He was born in Menomonie, Wisconsin, and spent the greater part of his career in studying and advancing the public health. His experience was a varied one following his graduation from the University of Michigan in 1905. He served with distinction in the Army Medical Corps of the United States from 1908 to 1935, when he retired to devote his entire time to public health. He became Epidemiologist in the Division of Tuberculosis of the Massachusetts Department of Public Health and a member of the Harvard Staff in 1935, and at the time of his death he was Associate Dean of the School of Public Health at Harvard and Professor of Public Health Practice.

Dr. Huber was an efficient organizer and administrator as well as a teacher. He had a keen interest in music, gardening and sports. His passing will be a great loss to his friends and associates and to all those who are concerned with the advancement of public health.

He is survived by his wife, Mrs. Frances Madison Huber and a daughter, Miss Lucille Huber.

CHESTER S. KEEFER, M.D., F.A.C.P.,
Governor for Massachusetts

DR. WILLIAM MASTIN SCOTT

Dr. William Mastin Scott, F.A.C.P., Shreveport, Louisiana, died of coronary artery occlusion on July 21, 1946. He is survived by his widow, Mrs. Margaret Sewall Scott; two sons, and three daughters.

Dr. Scott was born in Mobile, Alabama, June 21, 1900. He received his M.D. degree from Tulane University in 1923, and served his internship at the Highland Sanitarium in Shreveport. Following three years of general practice at Elm Grove, Louisiana, he moved to Shreveport and entered the field of internal medicine. As the years passed he came to occupy a prominent place among the leading internists of Louisiana, and both personally and professionally was held in high regard by his colleagues.

Dr. Scott became an Associate of the College in 1938, and was advanced to Fellowship in 1941. He was a regular attendant at the annual sessions of the College. He was active in the affairs of his Parish and State medical societies, and regularly attended the meetings of the Southern Medical Association, the American Medical Association, and the American Heart Association. A busy practice did not prevent faithful fulfillment of his duties as Visiting Physician to the Shreveport Charity Hospital.

EDGAR HULL, M.D., F.A.C.P.,
Governor for Louisiana

CAPT. EBEN ELLIOTT SMITH

Capt. Eben Elliott Smith, F.A.C.P., who retired from active service in the regular Navy of the United States on October 18, 1945, died June 16, 1946, after a service in the Navy of 28 years.

Capt. Smith was born in Dillsboro, Indiana, July 12, 1891. He received his B.S. degree from Moores Hill College, and his medical degree from Johns Hopkins University School of Medicine in 1917. He went directly into the Navy following medical school graduation, but at various times pursued postgraduate work at Rockefeller Institute, the U. S. Naval Medical School, the Mayo Clinic and New York Postgraduate Medical School. He had served on the faculty of the U. S. Naval Medical School, as Editor of the U. S. Naval Medical Bulletin and as officer in charge of the Division of Publications of the Bureau of Medicine and Surgery. His various assignments while in the Navy carried him over the world. He had been especially interested in medical editing, aviation medicine and pathology. He had been a Fellow of the American College of Physicians since 1927.

DR. JOHN DANIEL THOMAS

John Daniel Thomas, M.D., F.A.C.P., Washington, D. C., died July 15, 1946.

He was Emeritus Professor of Physical Medicine at Georgetown University School of Medicine and had practiced medicine in Washington for 50 years. He was a Life Member and Past President of the Medical Society of the District of Columbia.

Dr. Thomas was born in Northampton County, Virginia, August 13, 1868. He received his A.B. degree from Hampden-Sydney College in 1889, and his M.D. degree from the University of Virginia in 1892. He served an internship and residency at Gouverneur's Hospital, New York City, 1892-94. He did postgraduate work at the New York Postgraduate Hospital, and in Vienna. He served in the Spanish-American War, and was a Captain in the Medical Corps during World War I. He was on the medical staff of Emergency Hospital and the Washington Home for Incurables, visiting physician at Garfield and Georgetown Hospitals, and consulting physician at Mount Alto Hospital. He had been a consultant in Internal Medicine to the Diagnostic Center of the Veterans Administration, also to the Glenn Dale Sanatorium. He was Professor of Physical Medicine at Georgetown University School of Medicine for many years, becoming Professor Emeritus in 1924.

Dr. Thomas had been very active in the Medical Society of the District of Columbia, was a Fellow of the American Medical Association, a member of the Medical Society of Virginia, the Clinico-Pathological Society and the Metropolitan Club. He had been a Fellow of the American College of Physicians since 1924.

DR. GRANT SAMUEL BARNHART

Dr. Grant Samuel Barnhart, F.A.C.P., Washington, D. C., died recently. He was born in Lock Haven, Pa., September 11, 1868, went to Washington as a young man, receiving his medical degree from the old Columbian University in 1904. He practiced continuously in Washington since that time. For many years he was on the staff of the Washington Tubercular Dispensary. He was a member of the Medical Society of the District of Columbia, a Fellow of the American Medical Association, a Past President of the Washington Medical and Surgical Society, a charter member of the George Washington University Medical Society and the Washington Civitan Club. He had been a Fellow of the American College of Physicians since 1932. He was a 32nd degree Scottish Rite Mason and held many high offices in that organization. He was also affiliated with the Washington Board of Trade, Phi Sigma Kappa Fraternity and the Congressional Country Club.

DR. LOUIS VINCENT MCGOVERN

Louis Vincent McGovern, M.D., F.A.C.P., of Brooklyn, N. Y., was born in New York City, November 28, 1874. He received his premedical training at St. Francis Xavier's College, and was graduated from the University of Bellevue Medical College in 1902. Dr. McGovern died in Wyckoff Heights Hospital on April 29, 1946, at the age of 71 of hemiplegia. He was at one time lecturer on Diseases of the Lungs at the Long Island City College of Medicine; former Visiting Physician at St. Catherine's Hospital; also on the staff of Kings County Hospital. He was the author of several published papers, and a Fellow of the American College of Physicians since 1927. He had been certified by the American Board of Internal Medicine and was a member of the Kings County Medical Society.

ASA L. LINCOLN, M.D., F.A.C.P.,

Governor for Eastern New York

DR. CLARK ANSON WILCOX

Dr. Clark Anson Wilcox, F.A.C.P., of Wichita Falls, Texas, died on April 4, 1946, of aplastic anemia.

Dr. Wilcox was born in Scottsville, N. Y., February 7, 1890. He received his pre-medical training at the University of Michigan prior to obtaining his medical degree from the New York Medical College and Flower Hospital in New York City, where he graduated in 1916. He then served an internship at the Lying-In and Flower Hospital in New York, later having postgraduate work at Henry Ford Hospital, the Army Medical School, Cornell Medical College and Mayo Clinic. At one time Dr. Wilcox was assistant professor of chemistry and assistant roentgenologist at the New York Homeopathic Medical College. He served from 1920 to 1922 on the

faculty of the Army Medical School and the Army Dental School in Washington, D. C.

During World War I, Dr. Wilcox was commissioned first lieutenant in the Medical Reserve Corps of the U. S. Army, later accepting the commission of captain in the Medical Corps of the U. S. Army, from which he resigned to enter civilian practice in Wichita Falls, Texas. From 1923 until his death, he was radiologist with the Wichita Falls Clinic and Clinic-Hospital. He was a member of the American Medical Association, the Texas State Medical Association and the Wichita County Medical Society and served as vice president of the latter. He was a past president of the Texas Radiological Society. Dr. Wilcox was also a member of the Northwest Texas District Medical Association, the Radiological Society of North America, diplomate of the American Board of Radiology, and Fellow of the American College of Physicians since 1938. He was the author of numerous published papers.

Dr. Wilcox is survived by his widow, two daughters and a grandson. An earnest and conscientious physician, he will be missed by all with whom he came in contact.

M. D. LEVY, M.D., F.A.C.P.,
Governor for Texas

DR. BENJAMIN B. FOSTER

Dr. Benjamin B. Foster, F.A.C.P., died at his home in Portland, Maine, on May 8, 1946.

Dr. Foster was born in Portland on October 7, 1881. He attended the local public schools and the Vermont Episcopal Institute. He studied medicine at the Jefferson Medical College at Philadelphia and the College of Physicians and Surgeons at Boston, receiving his medical degree in the latter institution in 1906. He served an internship at the Boston City and Emergency Hospital and the Vanderbilt Clinic in New York City. He did special postgraduate work at the Vanderbilt Clinic in dermatology and syphilology. Dr. Foster's practice was confined to dermatology. In 1918 he organized the first clinic in Maine for the treatment of syphilis at the Maine Eye and Ear Infirmary; he had direct charge of this clinic until the beginning of his last illness in March of 1945. He was also Chief of the Department of Dermatology and Syphilology at the Maine General Hospital, until his retirement in 1945. For many years he conducted a weekly clinic in Dermatology at the Edward Mason Dispensary.

Dr. Foster became a Fellow of the American College of Physicians in 1930. He was also a member of the Portland Medical Club, the Cumberland County Medical Society, the Maine Medical Association, the Aegis Club, the Alpha Kappa Kappa Fraternity, and the New England Dermatological Society.

E. H. DRAKE, M.D., F.A.C.P.,
Governor for Maine

DR. LEON JUDAH SOLWAY

Dr. Leon Judah Solway, M.D., F.A.C.P., Toronto, Ontario, died December 14, 1945, his death not having been reported to the College until September, 1946.

Dr. Solway was born in Russia in 1885. He received his B.A. degree from the University of Toronto in 1907, and his M.B. degree from the same institution in 1909. He did postgraduate work in London, England, and had practiced for many years in Ontario. He was at one time assistant in Medicine at the University of Toronto, and on the staff of the Toronto General and the Toronto Western Hospitals. For the last several years he had been physician-in-chief, Mount Sinai Hospital.

Dr. Solway was a diplomate of the American Board of Internal Medicine, a member of the Toronto Academy of Medicine, the Ontario Medical Association, the Canadian Medical Association, and the American Heart Association. He had been a Fellow of the American College of Physicians since 1939, and a member of the Royal College of Physicians of London since 1922.

DR. WARD J. MACNEAL

Born at Fulton, Michigan, February 17, 1881; died in New York City, August 16, 1946.

Thursday, August 16, began as all days began for Dr. MacNeal within recent years. After breakfast he walked slowly to the Hospital. Having arrived at the laboratory, he gave his first attention to the routine work of the Hospital, saw some patients on the wards and on the private corridor who suffered from endocarditis or blood stream infections, reviewed the progress of the research on rheumatic fever that had arrived at a satisfactory conclusion, and finally dictated and signed a number of letters. It had been a pleasant and profitable morning's work, for the research on rheumatic fever after many years of discouragement at long last was drawing to a close in a highly satisfactory manner.

Leaving word that he would return at two o'clock, he walked home for lunch and his customary rest period. His wife had an unimportant social engagement and left happily to keep it as soon as the meal was completed. Soon after 2:00 p.m. the laboratory staff became worried at his failure to keep his appointment and after a suitable interval sent a messenger to his apartment. With the help of the house superintendent an entrance was effected. Dr. MacNeal had quietly died in his sleep. And so came to an end a typical day which was crowded with useful work and which might well be cited as typifying all the days of his adult life.

In December, 1918, Dr. MacNeal returned from nearly two years of service overseas with the United States Army in France to find his oldest son dying of bacterial endocarditis. It would appear that he made a pledge to himself to find at least some of the answers to the problem of bacterial

endocarditis and rheumatic fever. He made many and various approaches to these problems through succeeding years; the answer to bacterial endocarditis was successfully completed in the late thirties. It was not, however, until May of 1946 that he was able to announce the isolation of a virus from the blood stream of a child suffering from acute rheumatic fever that was capable of producing non-bacterial endocarditis in inoculated animals. This finding was duplicated in the following months in a number of cases of rheumatic fever. Personally he was wholly convinced that he had isolated the etiological factor causing rheumatic fever. It should be added, however, that Dr. MacNeal fully recognized the fact that there was still much work to be completed before the proof was all in hand for a positive announcement. Nevertheless it seems probable that his main task was completed except for the final publication which, after all, could be safely left in other hands, and so, having kept faith with his son, he quietly died.

Dr. MacNeal received his A.B. degree from the University of Michigan in 1901, his Ph.D. degree in 1904, his M.D. degree in 1905; in 1939 the University awarded him the honorary degree of Doctor of Science. He served as Fellow and instructor in bacteriology and histology at the University of Michigan (1901-06), instructor in anatomy and bacteriology at the University of West Virginia (1906-07), assistant professor of bacteriology at the University of Illinois (1907-11), and finally in 1912 became professor of pathology and bacteriology at the New York Post-Graduate Medical School and Hospital—a post he held for thirty-four years. For a time he was the medical adviser to the Josiah Macy Jr. Foundation. In the first World War he was on active duty in France, entering the Medical Corp as a Captain and receiving promotion to Major. His war service included a tour of duty with the American Trench Fever Commission, and he was for more than a year in command of the Central Laboratory at Dijon. His interest continued after the war, and he attained the rank of Colonel in the Medical Reserve Corp. It was only factors of personal health that kept him from active service in the second World War.

During his thirty-five years of active service at the New York Post-Graduate Medical School and Hospital, he served on the Board of Directors for three years (1921-24) and was vice chairman of the Medical Board for a number of years. His main task, however, at the Hospital was to find time outside routine duties to do research work. This meant a careful budgeting of his time and a complete lack of holidays or periods of relaxation. He did find time to do much of the investigation and the editorial work of the Thompson Pellagra Commission. The histological structure of the spleen engaged his interest, and the resulting publications became authoritative. Bacteriophages in his skilled hands became an effective agent before the days of the sulfa drugs and a valuable adjunct in treatment after their introduction. However, the problems of bacterial endocarditis and rheumatic fever were his chief recurring interests and will perhaps bring to his name enduring fame.

Dr. MacNeal was the author of "Studies in Nutrition" and the editor of the second edition of "Microorganisms." He was a valued member of many medical societies—his County, State and national associations, American College of Chest Physicians, New York Pathological Society, New York Academy of Medicine, Society of Experimental Biology and Medicine, Society of American Bacteriologists, American Society for Cancer Research and the American Association of Pathology and Bacteriology. He was a diplomate of the American Board of Internal Medicine, and had been a Fellow of the American College of Physicians since 1924. He had served as president of the New York Pathological Society and of the American Association for Cancer Research.

It can be written of Dr. MacNeal that honorary distinctions had for him little meaning unless they could be made to serve a useful and enlightening purpose. His outspoken honesty of opinion and his sense of duty were sometimes painful, if admirable, virtues to those who loved him most. He was a loyal friend and only with the greatest reluctance believed ill of those to whom he had once given his trust and confidence. He had a fine sense of humor, though it is to be feared that too few took time to find it out. His feeling of the importance of the job of living and a lack of convivial habits did not contribute to an easy acquaintance or set the stage for a passing moment of good fellowship. Probably the most satisfying moment in his life was that when he was able to assure himself with certainty that he had driven an entering wedge into the obscure story of rheumatic fever. The essentials of a task, set many years earlier, completed, it was not only typical but fitting that he should lay aside the burden of life. Those of us who knew Ward MacNeal best can hardly envisage him without an honest job on his mind and heart.

MARSHALL CARLETON PEASE, M.D., F.A.C.P.

DR. HYMAN I. SPECTOR

Hyman I. Spector, born July 15, 1894; died July 6, 1946. Associate Professor of Medicine, St. Louis University School of Medicine. Fellow of the American College of Physicians since 1938.

The death of Dr. Spector brought to a close an unusually useful life. Dr. Spector, during the course of twenty years, had taught many students who remember him with gratitude and who mourn his passing. He was exceptionally well endowed as a teacher, was devoted to his duties and displayed a background of high character which everyone felt and appreciated.

In his particular field of diseases of the chest, he attained national prominence. He published actively and was a zealous worker for the special organizations in his field. He was one of those teachers it is unusual to have in a medical school, but above all he was a sincere, honest and devoted Doctor.

Among the positions he held were: Past president, Mississippi Valley Conference on Tuberculosis; formerly vice president, St. Louis Tuberculosis Society, and chairman of the Committee on Industrial Health of the Missouri State Medical Association; chief, medical section, St. Louis Health Department from 1934 to 1943; at various times affiliated with Firmin Desloge Hospital, Mount St. Rose Tuberculosis Sanatorium, St. Mary's Hospital Koch Hospital, Jewish Hospital, and chest consultant, U. S. Marine Hospital, Kirkwood, Mo.; Fellow and former Regent, American College of Chest Physicians; member, Trudeau Society, American Public Health Association, and others; author of several published papers.

RALPH KINSELLA, M.D., F.A.C.P.,
Governor for Missouri.

DR. ISAAC HALL MANNING

Dr. Isaac Hall Manning, F.A.C.P., of Chapel Hill, North Carolina, was born in Pittsboro, North Carolina, September 14, 1866. He obtained his pre-medical training at the University of North Carolina; graduated in medicine from the Long Island College Hospital, Brooklyn, N. Y., 1897. He did postgraduate work at the University of Chicago and at Harvard Medical School.

Dr. Manning was Professor of Physiology at the University of North Carolina from 1901 to 1939. He was Dean of the School of Medicine from 1905 to 1933. He was Professor Emeritus of Physiology from 1939 to 1946.

Dr. Manning had been President of the Medical Society of North Carolina in 1933, President of the Hospital Savings Association of North Carolina, from the time of its organization in 1935 until 1942, when he became Chairman of the Board of Medical Directors. He was a member of the American Medical Association, a Fellow of the American College of Physicians since 1930. In 1940 the Alumni Association of the University of North Carolina School of Medicine honored him by presenting a portrait of him to the University. He died on February 12, 1946.

DR. ALANSON FILER BORT MORRIS

Dr. Alanson Filer Bort Morris, of Pittsburgh, Pa., an Associate of the College, died on February 6, 1946, in St. Stephen's School. Dr. Morris was an Associate of the College by virtue of membership in the old American Congress on Internal Medicine, which was merged with the College in 1926. He was born in 1868 and received his medical degree from the University of Pittsburgh School of Medicine in 1896. He served during World War I in the Medical Corps of the U. S. Army and was a Lieutenant Colonel in the Medical Reserve Corps thereafter. At one time he was first Vice President of the Allegheny County Medical Society. His death was due to coronary occlusion.

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OBSERVATIONS ON AMEBIASIS IN AMERICAN TROOPS STATIONED IN INDIA *

By GERALD KLATSKIN, M.D., *New Haven, Connecticut*

AMEBIASIS proved to be a serious problem in American troops stationed in India. Despite the institution of stringent sanitary control measures the incidence of infection with *E. histolytica* remained high and was responsible for a considerable loss of man-power through disability and hospitalization.

The clinical aspects of the disease were of great interest to medical officers. Although most of us had been well indoctrinated in the principles of recognition and control of the disease, few of us were prepared for its protean manifestations and many errors were made until we had become sufficiently conscious of the disease and familiar with its behavior.

Current literature and military directives led us to believe that therapy was a simple matter and that excellent results were to be expected, but experience with symptomatic and parasitologic relapses made it clear that the results of treatment left much to be desired.

The following report is based on observations made on 748 cases of amebiasis. Two hundred and eighteen of these were admitted to the U. S. Army Hospital in Calcutta during the period May 1943 through June 1944. The remaining 530 were admitted to the U. S. Army Hospital at Panagarh from July 1944 to February 1945.

CLINICAL MANIFESTATIONS

Intestinal Amebiasis. This diagnosis was adopted for all cases exhibiting *E. histolytica* in the stools. Since few cases had dysenteric symptoms, the term amebic dysentery was deemed inappropriate. The diagnosis carrier-state, *E. histolytica*, was not used because so many asymptomatic cases, discovered in routine surveys, when questioned carefully gave a history of intermittent diarrhea in the past. Moreover, it implied that the

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parasite was non-pathogenic for the host, a concept open to serious doubt. Of the 748 cases, 735 had intestinal amebiasis. The remaining 13 had hepatic amebiasis without *E. histolytica* in the stools.

In reviewing these cases it was difficult to classify them as asymptomatic, acute and chronic, since there had been no unanimity of opinion regarding the precise meaning of these qualifying terms and since so much depended on the accuracy of the past history. An analysis of 162 cases, in whom a careful and detailed history had been recorded, revealed that 84 per cent had recurrent bouts of diarrhea of varying severity and duration. In most cases these were mild to moderate in severity and of relatively short duration, usually two days to a week. There were no cases of continuous diarrhea over a long period of time. Two per cent of the cases had an acute dysentery of fairly rapid onset with blood and mucus in the stools and tenesmus. The remaining 14 per cent had no gastrointestinal symptoms. Much significance cannot be attached to the relative incidence of these asymptomatic cases, since their number was dependent on the extent to which routine stool surveys were done.

Diarrhea was the outstanding symptom in nearly all cases. Alternation of constipation and diarrhea was common, especially in the more chronic form of the disease.

As a rule the stools were mushy in consistency, bulky, foul-smelling and few in number. Commonly, the first stool occurred immediately after breakfast, was more watery than the others and was associated with urgency. In cases with an acute onset or an acute exacerbation the stools were watery, small in volume and numerous, and were indistinguishable from those seen in bacillary dysentery or acute enteritis. The stools usually contained a moderate amount of mucus but no gross blood or pus. Microscopically, a few red blood cells and an occasional leukocyte could be demonstrated. Gross blood was seen in the more acute forms of the disease. Several cases were admitted because of intermittent rectal bleeding without diarrhea. Their stools contained *E. histolytica*, but no ulcerations could be demonstrated on sigmoidoscopic examination. Since antiamebic therapy appeared to effect a cure, it was assumed that specific ulcers were present higher up.

Pus, usually demonstrable only by microscopic examination, was seen in many of the acute exacerbations and was interpreted as indicating a complicating bacillary infection, even when *Shigella* and *Salmonella* could not be cultured. Administration of sulfaguanidine almost invariably effected prompt, although incomplete, relief of symptoms.

Mild crampy pains, especially in the lower abdomen, were very common. In addition, many patients had vague digestive complaints suggestive of peptic ulcer or gall bladder disease. At times these symptoms dominated the clinical picture, but almost invariably a history of intermittent diarrhea could be obtained.

Slight afternoon elevations of temperature were often noted, but only rarely did they give rise to symptoms. The patients with acute dysentery

had moderate degrees of fever, but when the fever was high it almost invariably indicated a complication—amebic hepatitis, bacillary dysentery or malaria.

Headache, general malaise, lassitude, fatigability, weight loss, and other constitutional symptoms, often attributed to amebic infection,² were so common in troops stationed in this area for any length of time, it was our opinion they bore no relation to the disease. Moreover, eradication of the parasite rarely had any effect on these symptoms.

Dr. Krishnan, of the All-India Institute, called our attention to the association of urticaria and amebiasis, which is well recognized in India but which is rarely mentioned in text books³ or in the literature.⁴ We saw a good many patients with urticaria in whom *E. histolytica* were demonstrated. Forty per cent of the urticarias seen in the Calcutta hospital fell into this group.⁵ They presented several interesting features. None of the patients gave a history of allergic manifestations in the past or had a familial history of allergy. The rash was usually extensive and was often associated with angioneurotic edema. Diarrhea was a frequent accompanying symptom. Although the rash tended to recur despite intensive epinephrine therapy and dietary restriction, eradication of *E. histolytica* by specific chemotherapy almost always effected complete and permanent cure. Napier³ is of the opinion that these allergic phenomena are indicative of absorption of allergens through amebic ulcerations. The colonic symptoms were very mild in most cases and completely lacking in others, so that the presence of extensive ulceration was unlikely. Moreover, allergic phenomena were not seen in cases with extensive ulceration of the colon due to other causes, so that it is reasonable to suppose that, when they occurred in amebiasis, they were indicative of sensitization to *E. histolytica* or its by-products, rather than to absorption of allergens from the bowel contents.

Many cases exhibited slight to moderate tenderness and thickening of the colon, especially in the region of the cecum and the sigmoid. The remainder of the physical examination usually revealed nothing of note.

Hepatic Amebiasis. Sixty-nine of our cases had amebiasis of the liver. A detailed analysis of these cases has already been reported elsewhere,⁶ so that our findings will be summarized briefly.

The cases fell into the following four groups which had distinctive clinical features:

Acute abscess.....	7 cases
Acute hepatitis.....	16 cases
Subacute hepatitis.....	32 cases
Chronic hepatitis.....	7 cases

The abscess cases were characterized by liver pain, high fever, leukocytosis and a definite mass in the liver demonstrable either by palpation or by roentgen examination. Cough and abnormal pulmonary findings were common. The acute hepatitis cases were very similar, but no mass could be

demonstrated in the liver, the fever was less marked, pulmonary symptoms and findings were less common and the leukocyte count was lower.

The subacute hepatitis cases had enlarged tender livers, but only half of them complained of liver pain. Fever was inconstant and when present was low grade in character and intermittent. Pulmonary findings and leukocytosis were infrequent. Diarrhea was common and was often the outstanding complaint.

In contrast to the other groups, in which symptoms were usually present for less than 10 days, the chronic hepatitis cases were admitted with liver pain of long duration, ranging from two to 12 months. The symptoms and findings were otherwise similar to those in the subacute hepatitis group.

Pain, the outstanding symptom in all four groups, had a number of distinctive features, which, when carefully analyzed, usually indicated the liver and excluded other structures above and below the diaphragm as its source. These were very important in differential diagnosis. The pain was usually localized beneath the right costal margin or in the right lower chest. It was aching in character, was aggravated by inspiration, cough, change in position and jarring, and frequently radiated to the chest, shoulder, and lumbar region. Compression tenderness of the right lower chest proved to be a very valuable diagnostic sign. Although not considered pathognomonic of hepatic amebiasis, it was an important confirmatory finding and in a few instances made early diagnosis possible in the absence of other signs.

Although only 13 per cent of these cases had a definite history of intestinal amebiasis in the past, 63 per cent had had intermittent diarrhea suggestive of the disease, and 80 per cent were found to have *E. histolytica* in the stools on admission to the hospital.

Early diagnosis, extremely important in prognosis, depended chiefly on a careful analysis of the symptoms and physical findings. Roentgen and laboratory examinations yielded helpful collateral evidence, but were rarely diagnostic. Confirmation usually rested on the prompt specific response to emetine therapy. More direct confirmation requires the demonstration of *E. histolytica* in the liver, which is possible only in the later stages of the disease when an abscess has developed. Even then the parasite may be difficult to find, and it necessitates aspiration of the liver, a procedure not without danger and one found to be unnecessary in early cases.

All cases were treated with emetine alone and 68 of the 69 were cured. The remaining case was greatly improved but failed to meet the rigid criteria of cure laid down. It was our opinion that most cases of hepatic amebiasis could be cured without aspiration if recognized early and treated with sufficient emetine.

Amebic Appendicitis. Amebic ulceration of the cecum frequently gives rise to symptoms suggesting appendicitis.^{2, 7} In our experience, pain in the right lower quadrant was common, but a history of intermittent diarrhea and the finding of a slightly tender, thickened cecum without signs of peritoneal irritation, fever or leukocytosis usually suggested the true nature of the dis-

ease, and the demonstration of *E. histolytica* in the stools confirmed it. Emetine and carbarsone therapy usually effected a prompt cure.

We also saw a number of patients with the classical symptoms and physical findings of acute appendicitis who had *E. histolytica* in the stools. At operation the appendix showed inflammation, varying in degree from acute catarrh to acute suppuration with gangrene. On section, a few showed typical amebic ulcerations but many more exhibited motile trophozoites of *E. histolytica* in scrapings from the lumen. At the Panagarh hospital, where all appendices removed at operation were examined for amebae, one-third were found to harbor *E. histolytica*.⁸

These findings raise several interesting questions. Were these all amebic appendicitis or were we dealing with simple acute appendicitis complicating intestinal amebiasis? Were there any distinctive clinical features of amebic appendicitis, and was appendectomy justified in the face of known intestinal amebiasis?

Obviously, those with appendices exhibiting typical ulcerations and trophozoites had amebic appendicitis. It is difficult, however, to assess the rôle of the ameba in producing acute appendicitis in those without ulceration. Although the amebae could have been passive inhabitants from the cecum, the presence of the trophozoite form suggests that the parasite had actually invaded the mucosa. Unfortunately, histologic sections were not available to establish this point. It seems probable, however, that if microscopic amebic ulcerations were present they were not primarily responsible for the acute inflammation, but opened avenues for secondary bacterial infection.

The clinical course and findings in these cases were identical with those in non-amebic acute appendicitis, but a history of amebiasis, intermittent diarrhea or recurrent bouts of right lower quadrant pain suggested the correct diagnosis. In those with active diarrhea, *E. histolytica* were usually found in the stools preoperatively. In others they were demonstrated post-operatively.

Many authorities believe that surgical intervention is contraindicated in intestinal amebiasis with the appendicitis syndrome, unless emetine therapy fails, and that appendectomy may lead to disastrous results.¹ Operation is obviously unnecessary when the symptoms are due to amebic ulceration of the cecum, and it has been amply demonstrated that the post-operative mortality is high when the process is acute.

In our experience, limited largely to mild and moderate intestinal amebiasis, the symptoms referable to the cecum could usually be differentiated from those of acute appendicitis. When the classical signs and symptoms of acute appendicitis were present, however, they usually increased under emetine and carbarsone therapy and appendectomy had to be performed. A surprising number of patients developed acute appendicitis in the hospital while under treatment for intestinal amebiasis. At operation the cecum was often slightly thickened and inflamed, but the appendix was almost invariably the site of acute inflammation and obviously the seat of the trouble.

The post-operative course of our patients was uneventful, and we saw none of the complications seen in cases with acute amebic dysentery which had been mistakenly operated on for appendicitis. All our cases were started on emetine and carbarsone as soon as *E. histolytica* were demonstrated, which may, in part, account for our good results.

Other Forms of Amebiasis. One patient had an amebic ulceration of the skin. He was admitted with mild diarrhea and a painful ulcer of the perianal skin about 2 cm. in diameter. Trophozoites of *E. histolytica* were recovered from scrapings of the base of the ulcer and from the stools. The ulcer had previously been treated with a number of local medications without effect. It healed rapidly under emetine and carbarsone therapy.

Another patient had a most unusual complication—an amebic ulceration of the gall bladder. He was admitted with high fever, pain in the right upper quadrant and diarrhea. On examination he was found to have an enlarged tender liver, leukocytosis and *E. histolytica* in the stools. A diagnosis of acute amebic hepatitis was made and emetine therapy instituted. The following day routine malaria smears were found to be positive for *P. vivax* and quinine therapy was started. Despite this treatment the patient's condition grew worse. Pain and fever increased, the white blood cell count rose and he developed signs of peritoneal irritation over the gall bladder area. A diagnosis of acute cholecystitis or perforating amebic abscess was made and surgical exploration recommended. At operation a large acutely inflamed gall bladder, distended with pus, was removed. The liver was enlarged and engorged, but there was no evidence of abscess. On opening the gall bladder a deep punched-out ulcer was seen in the fundus. Scrapings from the base revealed actively motile trophozoites of *E. histolytica*. Unfortunately, reports on the culture of the pus and the histologic sections are not available. The post-operative course was stormy, but the patient ultimately recovered on emetine therapy. It seems probable that this patient had both acute amebic cholecystitis and acute amebic hepatitis, complicated by malaria.

A number of presumable cured cases of intestinal amebiasis returned to the hospital with a recurrence of diarrhea and cramps. Repeated stool examinations failed to demonstrate *E. histolytica*. Proctoscopic examination disclosed no mucosal changes, and roentgen studies of the colon were negative. A therapeutic trial of emetine, carbarsone and retention enemas of chiniofon cured about 10 per cent of these patients. A few of the patients were apparently cured following a prolonged course of sulfaguanidine in high dosage, but the remainder resisted all therapeutic measures and had to be evacuated to the Zone of the Interior with a diagnosis of "post-amebic colitis."

Rappaport⁹ has recently studied a group of resistant chronic diarrheas, which were initiated by amebic or bacillary dysentery, and made the interesting observation that many of them had had allergic manifestations in the past and exhibited sensitivity to food allergens, especially milk, chocolate

and wheat. Removal of these items from the diet resulted in prompt and permanent cure of the diarrhea and cramps. Most of these patients had previously been treated by a variety of methods without relief. After a symptom-free interval of several weeks a tube was introduced into the stomach and, without the patient's knowledge, the offending food was injected. This invariably resulted in a recurrence of symptoms. There seems little doubt, then, that post-amebic colitis is due to the development of food allergy in some instances.

DIAGNOSTIC METHODS

Stool Examination. Gross inspection of the stools was of little help. Diagnosis depended on the demonstration of *E. histolytica* cysts or trophozoites microscopically. In our experience, the most reliable and rapid technique was the examination of the second, fourth and sixth stools passed after a large saline purge, one ounce of magnesium sulfate crystals in a glass of water. Occasionally patients required a larger dose. The purge was omitted when active diarrhea was present. The stools were collected in pasteboard sputum cups and examined within 15 minutes. A thin saline suspension of each specimen was examined unstained. Whenever possible a fleck of mucus or blood was used in preparing the suspension. In most cases typical actively motile trophozoites of *E. histolytica* were demonstrated in one of the three specimens. When they were not, suspensions stained with dilute iodine solution were examined for cysts. In a few cases concentration methods were employed, but they were time-consuming and rarely demonstrated cysts when the first three direct smears were negative. When the first series of stools failed to reveal cysts or trophozoites, a second purge was administered after an interval of three or four days. It was a curious fact, confirmed repeatedly, that following a purge, trophozoites could not be demonstrated again for several days.

The only cellular elements seen were a few red blood cells and an occasional leukocyte. When the latter were present in any numbers, it was assumed that secondary bacterial infection was present, although pathogenic bacilli were rarely recovered on culture. Charcot-Leyden crystals were extremely rare.

Proctoscopy. Proctoscopic examination was, for a time, carried out in all cases of suspected amebiasis at Panagarh, but was abandoned as a routine procedure because it was time-consuming and added so little information. Not more than one-third of the cases exhibited mucosal changes, and in many these were not sufficiently characteristic to warrant a diagnosis of amebiasis. Direct smears from the mucosa were frequently positive for *E. histolytica*, but only rarely were they positive when the three purged stools were negative. Proctoscopy was useful in excluding other conditions when symptoms resisted specific treatment, and in following the progress of the more chronic forms of the disease with ulceration requiring local therapy.

Roentgen Examination. Barium enemas were done in a number of cases of intestinal amebiasis. Significant changes were rarely found and the procedure was considered of value only in excluding non-amebic lesions when symptoms failed to respond to specific therapy.

Roentgen examination of the lungs and diaphragm was of limited value in the diagnosis of early amebiasis of the liver. The diagnostic changes in the diaphragm¹⁰ occur only in the more advanced stages of the disease and are not seen when the liver is enlarged chiefly anteriorly and inferiorly.¹¹ Thirty-one per cent of our cases of hepatic amebiasis showed changes in the diaphragm—minor degrees of elevation, flattening and limitation of motion—but only one case had a localized bulge. Thirty-three per cent exhibited pulmonary changes at the right base, chiefly increased markings and haziness, and one case had a slight pleural effusion. These findings often suggested early pneumonia, the one condition most difficult to differentiate from acute amebic hepatitis and abscess, so that the roentgenograms were often misleading.

Roentgen-ray examination of the abdomen was of no value in determining liver size. In a group of 14 cases with easily palpable enlarged tender livers, roentgenograms demonstrated enlargement in only four.

Blood Studies. The white blood cell count was usually normal in intestinal amebiasis. Slight leukocytosis occurred in the acute form of the disease, but when it was much over 10,000 it invariably indicated a complication—usually amebiasis of the liver or bacillary dysentery. The average count in acute amebic abscess of the liver was 15,964 and in acute amebic hepatitis 12,215. Characteristically in these two conditions the relative polymorphonuclear count was only slightly increased. It averaged 83 per cent in the former and 72 per cent in the latter. This point was of considerable aid in differential diagnosis, as first pointed out by Rogers.¹²

Significant eosinophilia was rare, even in those complicated by urticaria. There were no anemias that could be attributed to amebiasis.

The sedimentation rate was elevated in 81 per cent of the cases with hepatic amebiasis and was found to be of great value in following the course of treatment. It remained elevated long after the other signs of activity had subsided and was an indication for further emetine therapy, for, when this was neglected relapse usually occurred. The sedimentation rate was rarely elevated in intestinal amebiasis, although it was noted that following the first few injections of emetine it occasionally rose slightly above normal.

TREATMENT

The results of treatment are difficult to evaluate in a disease like amebiasis which undergoes spontaneous remissions and in which it is almost impossible to differentiate between relapses and reinfections. It is even more difficult to compare the results of any two investigators since the disease varies so much in different parts of the world, since there are no standard criteria of

cure, and since so much depends on the length of the follow-up period, the skill of the microscopist and the number and technic of stool examinations.

The Rôle of Emetine. When emetine was introduced in the therapy of amebiasis,¹³ it was hailed as a specific curative agent. Its dramatic effect in relieving the symptoms of amebic dysentery has been amply confirmed, but experience has indicated it frequently fails to cure.¹⁴ Moreover, serious toxic reactions to the drug have been described. As a result, the rôle of emetine therapy in intestinal amebiasis has undergone a change. Current opinion limits its use to the control of symptoms and favors the newer iodine and arsenic compounds for eradication of the parasite.¹⁴ Some workers have abandoned emetine completely and rely on the iodine compounds alone.¹⁵

There is good reason to question the wisdom of relegating emetine therapy to the secondary rôle it now plays. The prompt and complete cure of amebiasis of the liver⁶ proves beyond doubt that under certain circumstances emetine is capable of eradicating *E. histolytica*. Moreover, remarkably good results have been reported in intestinal amebiasis when large doses of emetine have been employed.¹⁶ No doubt the fear of toxic effects has limited the dose of the drug used and accounts in part for the poor results obtained. It must be conceded, however, that even when large doses of emetine are employed there will be some failures.

The reasons for these failures are worthy of consideration. Since it is the cyst form of *E. histolytica* which persists, it has been suggested that failures are due to emetine's inability to destroy cysts.^{17, 18} This explanation is not acceptable. Cysts are non-pathogenic to the host, and there is no evidence that there are free-living trophozoites capable of producing cysts without invading the mucosa. The failure of cysts to disappear from the stools must indicate that emetine has failed to destroy all the trophozoites of *E. histolytica* in the tissues.

Manson-Bahr is of the opinion that the trophozoites become emetine-resistant.¹⁹ This view is supported by in vitro experiments on *E. histolytica* cultures, which, by gradual adaptation to increasing strengths of emetine solution, can be made to thrive in lethal concentrations.²⁰ Yet, Manson-Bahr's own work on the effectiveness of oral emetine-bismuth-iodide in resistant cases¹⁹ seems to contradict this theory.

The ability of emetine to destroy amebae more thoroughly in the liver than in the intestine may be related to differences in their circulation. In the liver, with its rich blood supply, amebicidal concentrations are readily attained and diffused with safe doses of emetine, but they may not be in chronically ulcerated areas in the intestinal mucosa in which the circulation has been impeded by fibrosis and inflammatory exudate. If this were true, larger doses of emetine ought to be effective. Chopra and Ghosh's work¹⁶ lends support to this view. They found that a high cure rate could be attained with 12 to 15 grains of emetine, but that doses of less than nine grains almost invariably resulted in relapses.

It seems clear, then, that emetine is an effective amebicidal agent, but that

in intestinal amebiasis the dose required for cure may fall into the toxic range. The problem, then, is whether emetine should be supplemented with amebicidal drugs or replaced by them.

Results of Treatment. Circumstances beyond our control made it impossible to conduct any long term experiments, but conditions were such in the Panagarh area that reliable, although admittedly incomplete, data could be gathered on the effectiveness of treatment. The organizations in this area were in fixed installations and had few changes in personnel during the period of this study. Most of them had dispensaries equipped to do stool examinations, and their medical officers were alert to the problem of amebiasis. Patients leaving the hospital following treatment were advised to report any recurrence of gastrointestinal symptoms to their medical officers, and were usually returned promptly for observation and treatment. At some stations routine follow-up stool examinations were done at monthly intervals. This was especially true of food handlers.

This study, based solely on hospital cases, affords fairly accurate data on the symptomatic but not on the parasitologic relapse rate, so that our cure rates are not strictly comparable to those of others who have checked the stools of their subjects routinely over long periods. Nevertheless, this type of study is well suited to a comparison of the results of treatment by various methods in large groups of patients.

Two groups were studied. The first, consisting of 355 successive cases of intestinal amebiasis, was treated in accordance with the principles laid down in a War Department circular on tropical diseases.²¹ Asymptomatic cases were given carbarsone, 0.25 gm. three times daily for one week and discharged from the hospital if three normally passed stools were negative for *E. histolytica*. They then took Diodoquin, 0.63 gm. t.i.d., or chiniofon, 0.6 to 1.0 gm. t.i.d., for one week on a duty status. Symptomatic cases were given the same treatment plus enough emetine to control the symptoms, rarely more than four grains. Retention enemas of carbarsone or chiniofon were seldom used except in patients with tenesmus or demonstrable ulcers in the lower colon. The relapse rate on this regime was 9.6 per cent.

In an effort to cut down on the relapse rate, a second group of 162 successive cases was treated by a new regime which included the routine use of a minimum of six grains of emetine, the more extensive use of chiniofon and carbarsone retention enemas and the adoption of more rigid criteria of cure. As a result the relapse rate was lowered to 5.6 per cent.

The basic course of treatment given to all patients, irrespective of symptoms, included injections of emetine, one grain daily for six days, and carbarsone, 0.25 gm. t.i.d., for one week, given concurrently. Following the last injection of emetine a purge was administered and three stools examined as outlined above. If these were negative the patient was discharged from the hospital and given Diodoquin, 0.63 gm. t.i.d., for one week on an ambulatory basis.

If the stools were positive or if symptoms persisted, the patient was

retained in the hospital and given a course of Diodoquin plus nightly retention enemas of 2 per cent chiniofon, usually 5 of 200 c.c. each. Those with symptoms also received additional emetine until they subsided or until a total of 12 grains had been given. At the end of the second week's treatment the stools were reexamined after a purge. If they were negative for *E. histolytica* the patient was discharged from the hospital and given vioform, 0.25 gm. t.i.d., for one week on an ambulatory basis.

If the stools were positive or if symptoms persisted, the patient was retained and given a course of vioform and five nightly retention enemas of 1 per cent carbarsone in sodium bicarbonate solution. The stools were checked for amebae at the end of the week, and, if negative, the patient was discharged and given another course of oral carbarsone to be taken on an ambulatory status.

Only one patient required a fourth week of treatment before his stools became negative. One hundred thirty-three cases had negative stools at the end of the first week, 24 at the end of the second, and four at the end of the third week.

The following is a tabulation of the treatment employed:

Emetine	
(a) 6 grains.....	119 cases
(b) 7 to 12 grains.....	43 cases
Carbarsone.....	160 cases
Diodoquin.....	156 cases
Vioform.....	25 cases
Chiniofon.....	2 cases
Retention enemas	
(a) chiniofon.....	30 cases
(b) carbarsone.....	9 cases

An attempt was made to study the nine relapses that occurred in this group of 162 cases, but the number was too small to demonstrate any significant relationship between relapse and the severity or duration of the disease before treatment or the amount of treatment it took to render the stools negative for *E. histolytica*.

The change in treatment, including the routine use of emetine, apparently effected a reduction in the relapse rate from 9.6 to 5.6 per cent. The significance of this improvement is still open to question, since the average period of observation for the first group was five months and for the second only 2.5 months. Nevertheless, there were other observations that appeared to confirm the impression that the routine use of emetine improved the end results of treatment. Many of the patients in the first group continued to experience gastrointestinal symptoms after treatment, but were not included as relapses, because *E. histolytica* could not be demonstrated in the stools. This was especially true of a large number of patients who had taken repeated courses of carbarsone and Diodoquin on an ambulatory status before coming to the hospital for treatment. Moreover, the only cases requiring evacuation to the Zone of the Interior because of the post-amebic colitis syndrome came from the group which had not received emetine routinely.

Obviously, more long range studies are needed to prove that the routine use of emetine improves the end results of carbarsone and Diodoquin therapy, but there are theoretical reasons for believing that it does, and the present study offers suggestive confirmation.

Hepatic Amebiasis. The dose of emetine required to cure hepatic amebiasis was dependent on the stage of the disease.⁹ Acute abscesses required an average of 21.9 grains, acute hepatitis 14.4 grains, subacute hepatitis 11.2 grains and chronic hepatitis 12.4 grains. The largest dose used was 27 grains, the smallest, six grains.

The criteria of cure adopted were: (1) complete absence of pain and fever, (2) absence of liver enlargement, (3) absence of subcostal and compression tenderness, and (4) normal leukocyte count and sedimentation rate.

Treatment consisted of 12 grains of emetine given over a 15 day period, one grain daily intramuscularly, with a three-day rest period after the sixth or ninth dose, depending on the patient's reaction to the drug. Most patients tolerated nine grains well, but a few complained of weakness or exhibited a fall in blood pressure after six grains. Following a three-day rest period, they were able to complete the 12 grain course with no ill effects.

The first course of emetine was followed by a two-week rest period, at the end of which emetine therapy was resumed. Courses of six grains each were then alternated with two-week rest periods until the criteria of cure were met.

The two-week rest period proved to be sufficiently long to prevent the cumulative toxic effects of the drug. In a few of the more acute cases the second and third courses of emetine were given at 8 or 10 day intervals with no untoward effects.

This treatment was supplemented with alternating courses of Diodoquin and carbarsone to eradicate the associated intestinal amebiasis, presumed to be present in all cases. Diodoquin was usually given first to avoid the possible toxic effects of arsenic on the liver, although none was seen in the few cases in which carbarsone was given first.

Toxicity. The cumulative toxic effects of emetine are well known. Among these may be mentioned disorders of the gastrointestinal tract, the cardiovascular system and the neuromuscular system. Their occurrence is dependent on the total dose employed, the route of administration, the duration of rest periods, the preëxistence of cardiovascular or renal disease and individual susceptibility to the drug.

The reports of death following therapy^{22, 23, 24} warrant a healthy respect for emetine, but the dangers attending its use have been exaggerated. Armed with a knowledge of the early toxic effects and the necessity for a few simple precautions, the clinician may employ this useful drug in moderate to large doses with safety. Most fatalities have followed the continued administration of large doses of emetine after the early signs of toxicity had appeared.

In our experience with over 500 cases treated with emetine, only one serious complication occurred. In that case, a young nurse with acute

amebic hepatitis, the ward officer failed to follow the treatment schedule outlined above and, as a result, the patient incurred a severe myocarditis, which was still evident both clinically and by electrocardiography one year later.

All patients on emetine were kept at strict bed rest. The blood pressure was determined twice a day and the pulse rate every four hours. The patients were carefully questioned daily about toxic effects, an important precaution, since patients frequently fail to report what to them are insignificant symptoms.

The intramuscular route of administration was used exclusively, because of the reported greater toxicity of the intravenous route.^{16, 25} Almost all patients had pain and tenderness at the site of injection, but only rarely were there any signs of local inflammation. The pain presented a number of interesting features. In a few individuals it was noted almost immediately after injection and disappeared in a few hours, but in the others the pain did not appear until a day or two later. Then, in addition to local tenderness, there was poorly localized, constant aching of the injected muscle, or more commonly, of all the surrounding muscles. The aching and tenderness usually lasted for several days to a week after treatment was stopped. Another interesting observation was that when emetine was injected into a number of sites, pain and tenderness did not occur in all of them. Sometimes it was possible to give as many as six injections into the same site with very little pain, while a single injection into the contralateral muscle caused severe pain which lasted for as long as two weeks. Emetine was never discontinued because of pain, but new sites of injection were chosen.

The appearance of mild diarrhea, or a slight increase if it was already present, was fairly common after five or six injections. It usually disappeared during the three-day rest period after the sixth or ninth emetine, and did not recur when emetine injections were resumed. In general, emetine was given in the face of mild diarrhea, but was stopped if it appeared to be increasing or if it was associated with other signs of toxicity.

Occasional patients exhibited a fall in blood pressure, rarely more than 15 or 20 mm. of mercury, which usually occurred between the sixth and ninth doses. This was taken as an indication for a three-day rest period, at the end of which emetine therapy was resumed with no ill effects. If the blood pressure failed to return to normal, which occurred only rarely, emetine therapy was discontinued. In several patients, whose blood pressures were low before treatment and who were debilitated, the daily dose of emetine was reduced to one-half or two-thirds of a grain. In our amebic hepatitis cases, who received the largest total doses, no significant changes in blood pressure were noted late in therapy.

Inconstant tachycardia, rarely more than 90 per minute, occurred in many patients. It did not appear to be regularly associated with changes in blood pressure and was not considered an indication for stopping emetine. In

the patient who developed myocarditis, there was persistent marked tachycardia with extrasystoles.

Unfortunately, electrocardiograms were not available as a routine procedure, so that we have no data on most of these patients. However, we have recently been carrying on a detailed study of emetine toxicity with frequent electrocardiograms, and find that minor myocardial changes are common with the dosage employed in this series, but that they are reversible and quickly return to normal when emetine is discontinued. Furthermore, it appears from this investigation that the rest periods recommended in our high-dose schedule afford an ample margin of safety. Obviously if electrocardiograms are available they should be employed before and during the course of therapy.

With the exception of the case of myocarditis, none of our patients had cardiac complaints, and the physical examination of the heart remained normal throughout treatment.

A few patients on the high-dose schedule complained of generalized weakness which appeared to be unrelated to changes in blood pressure or pulse rate, and which was not associated with demonstrable muscular weakness or other signs of neuritis. When weakness was more than minimal in degree, emetine was discontinued for a few days with prompt return to normal. In our recent work with large doses of emetine, several patients have developed muscle pain and tenderness associated with muscular weakness, especially in the calves, neck and forearms. The symptoms and physical findings were identical with those said to occur in emetine-neuritis,²⁶ but we were never able to demonstrate reflex changes, sensory disturbances or muscular atrophy. It was our impression that these were examples of emetine-myositis. This problem is being investigated further.

In summary, then, only one serious complication of emetine therapy occurred in over 500 cases. Of the milder toxic manifestations, mild diarrhea, transient tachycardia and a slight fall in blood pressure were fairly common, while generalized weakness occurred occasionally, especially after large doses. The persistence of any of these symptoms for more than one day was an indication for discontinuing emetine therapy, but it could be resumed after an appropriate interval without ill effects.

No significant toxic effects of carbarsone, Diodoquin or vioform were noted. Chiniofon invariably induced diarrhea when the recommended dose of 1.0 gm. t.i.d. was given. Very few patients could tolerate more than 0.8 gm.

SUMMARY

1. Observations on the clinical manifestations and treatment of 748 cases of amebiasis, seen in American troops stationed in India, have been summarized.

2. The outstanding clinical features of intestinal amebiasis were mild to

moderate, intermittent diarrhea, often accompanied by other gastrointestinal symptoms, but rarely associated with any constitutional reaction.

3. Amebiasis was a common cause of urticaria and angioneurotic edema in India.

4. Amebiasis of the liver was a common complication, and varied in severity from an acute abscess to a low grade chronic hepatitis. Emetine alone cured 68 of the 69 cases.

5. The relation of appendicitis to amebiasis was discussed. In some cases appendicitis appeared to be due directly to the ameba, while in others it appeared probable that the ameba had played a secondary rôle in opening avenues for bacterial infection.

6. The simplest and most reliable diagnostic procedure in our experience was the demonstration of the trophozoites of *E. histolytica* in fresh stools passed after a large saline purge.

7. Evidence was presented which suggests that the routine administration of moderate doses of emetine improved the end results of treatment with chiniofon, carbarsone and Diodoquin.

8. Serious toxic reactions were rare, even with large doses of emetine, when the patient was kept at bed rest and observed carefully. Treatment was stopped when the early signs of toxicity appeared, but was resumed after an appropriate rest period.

BIBLIOGRAPHY

1. STRONG, R. P.: Stitt's Diagnosis, prevention and treatment of tropical diseases, 1942, The Blakiston Co., Philadelphia.
2. D'ANTONI, J. S.: Amebiasis, recent concepts of its prevalence, symptomatology, diagnosis and treatment, Internat. Clin., 1942, 1, 100.
3. NAPIER, L. E.: The principles and practise of tropical medicine, 1943, Thacker, Spink and Co., Ltd., Calcutta, p. 434.
4. GIORDANO, A. F.: Urticaria and amebiasis, Abstr., Trop. Dis. Bull., 1945, xlii, 37.
5. COHEN, M.: Personal communication.
6. KLATSKIN, G.: Amebiasis of the liver, Ann. Int. Med., 1946, xxv, 601-631.
7. SAPERO, J. J.: Clinical studies in non-dysenteric intestinal amebiasis, Am. Jr. Trop. Med., 1939, xix, 497.
8. MILLER, D.: Personal communication.
9. RAPPAPORT, E. M.: Personal communication.
10. OCHSNER, A., and DE BAKEY, M.: Amebic hepatitis and hepatic abscess, Surgery, 1943, xiii, 460.
11. MUNK, J.: X-ray appearances in amebic hepatitis, Brit. Jr. Radiol., 1944, xvii, 48.
12. ROGERS, L.: Recent advances in tropical medicine, P. Blakiston's Son and Co., 1929, Philadelphia, p. 262.
13. ROGERS, L.: The rapid cure of amebic dysentery and hepatitis by hypodermic injections of soluble salts of emetine, Brit. Med. Jr., 1912, i, 1424.
14. FAUST, E. C.: Some modern conceptions of amebiasis, Science, 1944, xcix, 69.
15. D'ANTONI, J. S.: Further observations on amebic and bacillary colitis in the New Orleans area, Am. Jr. Trop. Med., 1943, xxiii, 237.
16. CHOPRA, R. N., and GHOSH, B. N.: The therapeutics of emetine, Indian Med. Gaz., 1922, lvii, 248.

17. MANSON-BAHR, P.: Amebic dysentery, facts and fallacies in radical treatment, Abst., Trop. Dis. Bull., 1945, xlii, 207.
18. BTESH, S.: On the treatment of chronic amebiasis, Abst., Trop. Dis. Bull., 1945, xlii, 128.
19. MANSON-BAHR, P.: Amebic dysentery and its effective treatment, Brit. Med. Jr., 1941, ii, 255.
20. HALAWANI, A.: Experimental study of resistance of *Entamoeba histolytica* to emetine hydrochloride in vitro, Ann. Trop. Med., 1930, xxiv, 273.
21. War Department, S. G. O. Circular Letter No. 33, Treatment and control of certain tropical diseases, February 2, 1943.
22. LEIBLY, F. J.: Fatal emetin poisoning due to cumulative action, in amebic dysentery, Am. Jr. Med. Sci., 1930, clxxix, 834.
23. LEVY, R. L., and ROWNTREE, L. G.: On the toxicity of various commercial preparations of emetin hydrochloride, Arch. Int. Med., 1916, xvii, 420.
24. JOHNSON, H. H., and MURPHY, J. A.: The toxic effect of emetine hydrochloride, Mil. Surg., 1917, xl, 58.
25. HEILIG, R., and VISVESWAR, S. K.: On the cardiac effects of emetine, Indian Med. Gaz., 1943, lxxviii, 419.
26. KILGORE, A. R.: Peripheral neuritis following emetin treatment of amebic dysentery, China Med. Jr., 1917, xxxi, 207.

THE MANAGEMENT OF AMEBIASIS*

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THE return of thousands of American troops from remote regions of the world where amebic dysentery is highly endemic makes it imperative that physicians throughout the United States acquaint themselves with the problems that arise in the diagnosis and treatment of this disease. To what proportions this menace might rise is indicated by the statistical reports from the comparatively small India-Burma Theater. Surveys of American troops in the Calcutta area reveal an incidence of amebiasis of 23 per cent.¹ In Myitkyina, Burma, 18.3 per cent of the troops were found to have the parasites in their stools.² When it is recalled that at the cessation of hostilities, there were nearly a quarter of a million soldiers in this theater, the number of potentially infested soldiers returning from this one small sector becomes significant.

To aid in this problem, we present some of the experiences in the diagnosis, treatment, and general management of amebiasis, as encountered in a large general hospital in Burma. Owing to the fact that the military situation prevented some of these patients from returning for periodic follow-up examinations and because others were followed for only three to five months, it is apparent that these observations can hardly be presented as a carefully controlled scientific study.

CLINICAL MATERIAL

Three hundred and sixty cases of amebiasis were studied for this report from among those admitted to the 18th General Hospital at Myitkyina, Burma. Most of these patients had been in this area for only a short time, which led us to believe that, in general, we were dealing with infections of relatively short duration. This may account for the mildness of symptoms, the lack of complications, and the generally good response to therapy.

HISTORY AND SYMPTOMS

Of the 360 patients, 140 denied all symptoms even when questioned specifically for them. Table 1 presents graphically the symptoms elicited from the other 220 patients. Twenty-one of these patients have a history of previously proved amebiasis. Only 120 of the symptomatic patients were ill enough to seek admittance to the hospital. The remaining 100 who gave a history of symptoms and the 140 non-symptomatic patients were hospital-

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ized after routine stool examinations revealed the presence of *E. histolytica*. Sixty-eight per cent of the symptomatic patients gave histories of less than one month's duration.

Abdominal pain varied considerably in location and severity. Frequently it was generalized, as found in any type of diarrhea. At other times, it was

TABLE I
Symptoms Elicited in 220 Cases of Amebic Dysentery

Abdominal pain...	210	95.4%
Diarrhea.....	184	83.6
Dyspepsia.....	112	50.9
Anorexia and malaise...	105	47.7
Recent weight loss.....	51	23.2
Fever.....	33	15.0
Nausea and vomiting..	19	8.6
Bloody stools.....	12	5.4

localized over some portion of the colon. For example, six cases were admitted as "appendicitis suspects." Another more common syndrome encountered in this group simulated that of peptic ulcer. So protean were the manifestations of amebiasis that any patient with gastrointestinal symptoms became a potential suspect.

Diarrhea varied from intermittent mushy stools to the severe fulminating variety seen in bacillary dysentery. That only 12 patients gave histories of bloody stools is qualified by the fact that the pit type latrine used in this area precluded proper inspection.

PHYSICAL EXAMINATION

The findings on physical examination are summarized in table 2.

TABLE II
Physical Findings in 360 Cases of Amebiasis

Colonic tenderness.....	225	62.5%
Compression or percussion tenderness over liver..	54	15.0
Enlarged tender liver.....	29	8.1
Enlarged non-tender liver....	2	0.6
Liver abscess....	1	0.3

Frequently no objective signs whatsoever were found. Only 33 soldiers had fever, but this was at times as high as 104° F. Concurrent bacillary infections in these patients were ruled out by negative stool cultures and dramatic response to anti-amebic therapy. Tenderness over some portion of the colon was a frequent physical finding, not only in the symptomatic but even in the asymptomatic group. At other times, the cecum or sigmoid were spastic and readily palpable. Compression or percussion tenderness over the liver was often present, even when there was no demonstrable hepatic enlargement. Since the majority of these cases were acute and apparently of short duration, weight loss could hardly be expected to be a common finding.

LABORATORY EXAMINATION

Stool examination is the only laboratory procedure of significance. The technic used is that described in the standard texts.^{3, 4} In almost all cases, a saline purgative was administered to produce a liquid stool, which was examined while still fresh.

Of the 360 soldiers in this series, 314 demonstrated trophozoites in their stools, 19 showed cysts, and 27 had both. There appeared to be no correlation between the severity of the disease and the stage of the parasites identified.

In the symptomatic group, 101 patients had rectal cultures taken on admission by the rectal swab technic. Nine of these grew members of the *Shigella* group. There were no pathogens isolated in the 68 cultures taken in the non-symptomatic group.

Nine hundred and seventy-eight individuals in the Myitkyina area were examined in three stool surveys. One hundred and seventy-eight of these demonstrated *Entameba histolytica*, an incidence of 18.3 per cent. The number of stools examined for each individual varied from one to six, as follows:

Positive on the first stool examination . . .	102	57.3%
Positive on the second stool examination	20	11.2
Positive on the third stool examination . .	27	15.2
Positive on the fourth stool examination	13	7.3
Positive on the fifth stool examination.	11	6.2
Positive on the sixth stool examination.	5	2.8

SIGMOIDOSCOPY

Table 3 summarizes the sigmoidoscopic findings in both the symptomatic and non-symptomatic groups.

TABLE III
Sigmoidoscopic Findings in 229 Cases of Amebiasis

Symptomatic group:	
Number sigmoidoscoped.	138
Normal mucosa	94
Mild to moderate changes	28
Severe changes	16
Asymptomatic group:	
Number sigmoidoscoped	91
Normal mucosa	78
Mild to moderate changes	11
Severe changes	2

Various degrees of hyperemia, punctate hemorrhages, or minute erosions were considered mild to moderate mucosal involvement. Severe changes consisted of the usual frank ulcerations seen in subacute and chronic cases.

The diagnosis was established in six cases by identifying the organism from smears made at sigmoidoscopy after repeated stools had been negative.

TREATMENT

All patients with positive stools, whether they showed cysts or trophozoites or whether or not symptoms were present, received a full course of treatment.

Emetine hydrochloride in doses of one grain daily was administered by deep subcutaneous injection for seven days. At the same time, the patient received 0.25 gm. of carbarsone three times daily for 10 days. If diarrhea was present, he was given a low residue diet. Symptoms were usually controlled by tincture of belladonna, paregoric, or powdered opium, but in severe cases codeine or morphine was occasionally necessary.

While receiving emetine, the patient was confined to bed. If myocardial damage was suspected or if the patient was over 40 years of age, electrocardiograms were taken before and during treatment. Blood pressures were checked twice daily. No electrocardiographic abnormalities were noted during emetine therapy.

On the eighth, ninth and tenth days of treatment, stools were examined for amebae. If they were negative and if the patient was asymptomatic or had only occasional mild symptoms, he was given 0.63 gm. of Diodoquin three times daily for 14 days. At the end of this time, stools were examined again.

After the completion of the emetine and carbarsone, if (1) the stools were still positive, (2) moderate to severe symptoms were still present, or (3) sigmoidoscopic examination still showed abnormal mucosa, the patient received vioform rather than Diodoquin, in doses of 0.25 gm. three times daily for 10 days. At the same time, chiniofon retention enemas were given on alternate days, according to the technic of Manson-Bahr.⁵ Occasionally a second course of three doses of emetine was given on the twelfth, thirteenth, and fourteenth days. In some cases in which symptoms persisted, the entire routine was repeated after a suitable rest period of three or four weeks. In general, if the symptoms did not respond to the first complete course of treatment, they did not improve on the second series of carbarsone, emetine and iodine preparations. If treatment failed and the patient could not do full duty, he was returned to the United States for further hospitalization.

On being discharged from the hospital, patients were cautioned to have their stools examined one and three months after concluding treatment.

Toxic manifestations in general were mild and infrequent. The following were attributed to emetine: generalized weakness, generalized muscle aching, diarrhea, nausea and vomiting (31 patients), palpitation and tachycardia (7 patients), foot drop (1 patient), and hematuria (1 patient).

Carbarsone, Diodoquin, and vioform were well tolerated. However, dyspepsia, nausea, vomiting, diarrhea, pruritus ani, furunculosis, and skin rash were encountered frequently enough to suggest that all are potentially toxic. The majority of the patients treated with chiniofon orally developed diarrhea, which at times was so severe that the drug had to be withdrawn.

Pain and local reactions were markedly decreased by injecting emetine by the deep subcutaneous rather than the intramuscular route. Generalized muscle aches seemed decreased when 10 mg. of thiamine chloride daily was included in the routine.

RESULTS

Without any opportunity for long follow-up study, the efficacy of these measures is difficult to evaluate. All but 14 of the 360 soldiers in this series were eventually returned to full duty. In reviewing the case histories of these 14 in whom symptoms persisted despite long treatment, several points become significant. The duration of their symptoms ranged from five to 14 months, in contrast to the great majority whose symptoms were present a month or less. Nine of these patients had had previous episodes of amebic dysentery. Of these, none had had either adequate treatment by present standards or follow-up stool examinations. Eleven had sigmoidoscopic findings which varied from mild hyperemia to frank ulceration.

There were 177 patients available for follow-up study three to five months after treatment. Of these, 84 had been in the symptomatic group. All had negative stools at monthly intervals and at the end of this time, but two still complained of abdominal cramping, three of cramping and occasional loose stools, two of pruritus ani, and one of marked asthenia. Of the 93 patients in the asymptomatic group who were followed for this period, all had negative stools for three to five months, but two who had never before had symptoms now complained of abdominal cramping and loose stools.

HEPATIC INVOLVEMENT

Thirty of the 360 patients were found to have enlargement of the liver at the time of admission, 26 of whom were in the symptomatic group and four of whom were in the non-symptomatic group. Two patients developed hepatomegaly while undergoing emetine therapy, an observation confirmed by at least two medical officers. Twenty-four additional patients had compression or percussion tenderness over the liver area, but did not demonstrate hepatomegaly.

Only one patient demonstrated enough clinical and roentgenological evidence to warrant a diagnosis of liver abscess. Although aspiration was contemplated because of an initially poor response to emetine, the subsequent rapid improvement made this procedure unnecessary. Positive stools were never found in this patient, and he did not have diarrhea.

When the liver was appreciably enlarged and tender, the patient was treated with 1 gm. of chiniofon three times daily for 14 days, rather than with carbarsone which we felt might be toxic. If chiniofon caused excessive diarrhea, vioform was substituted in doses of 0.25 gm. three times daily. Emetine was given in the usual manner except that the patient received a

course of 9 grains. If there was no satisfactory improvement, three more grains were given after a one week interval.

In 20 of the 30 cases with hepatomegaly, the liver promptly receded under this treatment, and tenderness disappeared. In three, the liver was still palpable, although considerably smaller after therapy. These patients were returned to duty because they were clinically well and showed no evidence of liver damage. The remaining seven were returned to the United States because of persistent hepatomegaly and symptoms referable either to the intestine or liver. It is significant that while only 8.6 per cent of the whole group had liver enlargement, 50 per cent of the group of 14 who could not return to duty showed this finding.

It is emphasized that the hepatic enlargement in these cases does not necessarily indicate actual amebic invasion of the liver. Napier has suggested that the entire picture may be caused by hepatic congestion, and that the response to emetine is due to the non-specific effect of the drug on congestion of the liver.⁶ Many writers, however, feel that these findings indicate a pre-suppurative stage of liver abscess, or multiple minute abscesses.^{7, 8, 9, 10} Whatever the mechanism may be, the dramatic results with emetine make it imperative to recognize hepatic involvement early so that the patient may have the advantage of prompt therapy.

DISCUSSION

The protean manifestations of amebiasis, while pointed out by many writers^{4, 5, 6} are emphasized by comparing the clinical findings in this series with those described elsewhere.¹¹ It seems apparent that such factors as dosage, race of parasite, concurrent bacterial infection, and duration of infection may greatly influence the symptomatology. At times it may be indistinguishable from bacillary dysentery. At other times, diarrhea may be completely lacking.²³

Physical examination may at times be entirely negative, but tenderness over some portion of the colon is constant enough to direct suspicion toward amebiasis. Compression or percussion tenderness over the liver area may indicate hepatic involvement even when the liver is not appreciably enlarged. It is interesting to observe that two patients who demonstrated that sign later developed hepatic enlargement while under treatment. That liver enlargement in amebiasis may not necessarily indicate actual invasion of the organ by the parasite has been pointed out.

Most laboratory workers in this area and elsewhere¹² agree that the administration of saline purgatives to produce a fluid stool facilitates the identification of trophozoites. For example, it was not a unique experience to identify trophozoites of *E. histolytica* in the fluid stool caused by the purge after vermifuge, where examination of the formed stool prior to treatment had revealed only hookworm ova. Others prefer to use a formed stool with flotation methods¹³ and various staining technics to identify the cystic

forms.¹⁴ In our experience, the increase in number of positive stools by using the flotation method was not significant enough to warrant the additional time required to perform the test. All amebae identified were of the small race variety, thought by some to be less pathogenic than the large race.

Special mention should be made of the value of stool surveys in hyperendemic areas to insure prompt diagnosis and treatment. Although there is no absolute evidence to show that all individuals who demonstrate parasites in their stools will develop clinical dysentery, there can be no way of foretelling who will be affected or how severe the clinical course may be. That extensive invasion can occur before symptoms appear is demonstrated by the large number of patients with amebic hepatitis who never have diarrhea and the significant number of asymptomatic patients in this series who demonstrated gross proctoscopic findings. For this reason, the use of surveys for early diagnosis appears desirable. Our experience with surveys suggests that for practical purposes, the examination of three stools for each individual will detect the parasite with an accuracy of approximately 85 per cent.

Sigmoidoscopy appears to be a valuable procedure in the management of amebiasis. In patients with diarrhea who have negative stools, amebae are identified from ulcers seen at sigmoidoscopy frequently enough to make the procedure valuable whenever the etiology is obscure. The appearance of the mucosa and its response to therapy may serve not only as a prognostic aid, but also may help to determine what type of regimen to undertake for further treatment.

The futility of attempting to treat amebic dysentery with any one drug is well recognized. Manson-Bahr has pointed out that hypodermic injections of emetine may not cure amebic dysentery because the drug is not excreted into the feces and does not come in contact with the pre-cystic forms.^{15, 16} Clinically, the use of repeated doses of this drug alone has proved a dismal failure.¹⁷ Such a procedure is not only dangerous because of the potential toxicity of the drug, but also because it may result in an emetine-fast strain of amebae. This has been corroborated in the laboratory by subjecting cultures of amebae repeatedly to emetine and then demonstrating its resistance to the drug.¹⁸

On the other hand, enough failures have been observed in this theater after using oral amebicides alone to suggest that the amount of absorption from the intestinal tract of drugs like carbarsone, Diodoquin, vioform, or chiniofon at times may not be sufficiently adequate to destroy those parasites that have invaded the tissues or the portal system. Emetine still appears to be the most effective drug in these cases. The opinion that no case of amebiasis should be treated with one drug or with even one group of drugs is supported by carefully controlled observations in a British General Hospital, where it was found that neither the iodine nor the arsenical preparations alone were capable of replacing emetine in the treatment of amebiasis.²⁴

Although it is acknowledged that emetine is potentially a dangerous drug, the incidence of toxic results when given in small doses with proper

precautions is so low that its use is rarely contraindicated. The oral amebicides with the exception of chiniofon caused but few distressing symptoms, but their potential toxicity has been pointed out.¹⁹

It has been the feeling in this hospital that the term "carrier" should be avoided. It is true that some writers believe that only a small percentage of individuals who demonstrate parasites in their stools actually have intestinal lesions. Others are convinced that there is always intestinal invasion even though the lesions be only microscopic. The evidence for and against each view is reviewed by Adams.²⁰ Certainly in our experience, it has been easy to demonstrate potentially destructive trophozoites by administering purgatives to asymptomatic cyst passers. The presence of ulceration in such patients is also evidence that the term carrier is deceptive and misleading. We feel strongly that every individual with *E. histolytica* in his stool has a potentially dangerous condition, whether or not symptoms are present, and should receive prompt and vigorous treatment. This view is advanced by Adams, who writes as follows: "It seems improper to neglect a detected infection until clinical manifestations make their appearance. To do so is to condemn many patients to subsequent unnecessary ill health with the possible development of a major disaster such as an amebic liver abscess. . . . I therefore think they should be regarded as latent cases requiring early treatment." For this reason, we have included emetine in the treatment of *all* patients who have amebae in their stools, whether these be cysts or trophozoites and whether symptoms are present or not.

Sufficient evidence is accumulating to show that bacteria may play a significant rôle in the pathogenesis of amebiasis.²¹ To support the experimental evidence that bacteria may enhance the pathogenicity or predispose to invasion is the not infrequent clinical observation that pus cells may be present in the stools of patients with amebic dysentery, even though stool cultures are negative. For this reason, patients in whom symptoms persist after adequate anti-amebic therapy often are benefited by a course of sulfadiazine.

The importance of follow-up stool examinations cannot be too greatly stressed. Too often the criteria for cure have been negative stools after seven to 10 days of treatment. Since it has been shown that cysts seldom appear in the stools until 10 to 20 days after treatment,²² the patient obviously should be followed for a period of months.

Several factors may determine the prognosis in amebic dysentery. The fact that in this series the parasites were of the small race may account for the relatively mild course most of the patients ran. Two significant findings were present in those patients who could not be returned to duty: (1) The duration of symptoms before diagnosis was made and treatment begun was very long. This clinical observation has been borne out by others,¹⁶ and suggests that the pathogenicity of amebae is enhanced by long existence in the human intestine. (2) Almost all patients of this group received inadequate treatment by present standards. This might suggest that suboptimal doses of amebicides may produce a drug-resistant strain of organism as some-

times occurs in bacterial infections inadequately treated with sulfonamides. Drug-fast strains may also be produced by repeated courses of the same amebicide.

CONCLUSIONS

1. The high incidence of amebiasis in American troops in the India-Burma Theater suggests that the disease may become a major health problem in the future.

2. The variation in symptomatology emphasizes that the disease must be considered in the differential diagnosis of any gastrointestinal ailment.

3. Physical examination may be entirely negative, but colonic tenderness should direct suspicion toward intestinal amebiasis and compression or percussion tenderness over the liver toward hepatic involvement.

4. Clinical differentiation of amebic from bacillary dysentery is not always possible. Stool examination by a trained and experienced laboratory technician is the only reliable means of diagnosis.

5. Sigmoidoscopy is sometimes a valuable diagnostic adjunct.

6. The large tender liver frequently observed in amebiasis, although not necessarily signifying a true amebic hepatitis, is frequently associated with the more severe infections.

7. The combined treatment of subcutaneous injections of emetine hydrochloride with oral amebicides is the most satisfactory regimen. The use of either form of treatment alone not only may be unsuccessful, but may actually be harmful by producing a drug-fast strain of parasite.

8. The term "asymptomatic carrier" is dangerous and misleading. It is our opinion that all individuals with amebiasis are diseased and, if treated at all, should be treated vigorously, not only with oral amebicides, but also with injections of emetine, because emetine (a) is the most effective amebicide for parasites that have penetrated the mucosal wall, (b) more effectively eradicates amebae that have penetrated into the portal system without yet producing symptoms, and (c) is comparatively non-toxic when given properly.

9. Sulfadiazine may sometimes be of value in relieving symptoms that persist after adequate anti-amebic therapy.

10. The importance of follow-up stool studies is stressed.

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BIBLIOGRAPHY

1. BLUMENTHAL, H. T., Major, M.C., Commanding Officer, 29th Medical Laboratory: Unpublished Data.
2. STEER, ARTHUR, Major, M.C., Chief of the Laboratory, 18th General Hospital: Unpublished Data.
3. STITT, E. R., CLOUGH, P. W., and CLOUGH, M. C.: Practical bacteriology, haematology, and animal parasitology, p. 413, 1942.

4. STRONG, R. P.: Stitt's Diagnosis, prevention, and treatment of tropical disease, p. 501, 510, 1943.
5. MANSON-BAHR, P.: The dysenteric disorders, 1939, p. 196.
6. NAPIER, L. EVARD: The principles and practices of tropical medicine, 1943, p. 444.
7. ROGERS, L.: Amebic liver abscess, *Lancet*, 1922, i, 463.
8. PALMER, REX E.: Changes in the liver in amebic dysentery with special reference to the origin of amebic abscess, *Arch. Path.*, 1938, xxv, 327.
9. MELENEY, HENRY E.: The pathology of amebiasis, *Jr. Am. Med. Assoc.*, 1934, ciii, 1213.
10. SODEMAN, W. A., and LEWIS, B. O.: Amebic hepatitis, *Am. Jr. Trop. Med.*, 1945, xxv, 35.
11. ROGERS, A. M., and ELSOM, K. A.: Amebiasis as seen in an army general hospital in Assam, *Field Med. Bull., USA, IBT*, 1945, iv, 316.
12. D'ANTONI, J. S.: Amebic and bacillary colitis in the New Orleans area, *Am. Jr. Trop. Med.*, 1942, xxii, 319.
13. FAUST, E. C., SAWITZ, W., TOBIE, J., ODOM, V., PERES, C., and LINCICOME, D.: Comparative efficiency of various techniques for the diagnosis of protozoa and helminth in feces, *Jr. Parasitol.*, 1939, xxv, 241.
14. PASCHAL, H. W.: A modified rapid staining technique for intestinal parasites, to be published.
15. MANSON-BAHR, P.: Amebic dysentery, *Lancet*, 1944, ii, 718.
16. MANSON-BAHR, P.: Treatment of amebic dysentery, *British Med. Jr.*, 1941, ii, 255.
17. LEISHMAN, A. W. D.: A year of military medicine in India, *Lancet*, 1944, ii, 231.
18. BARRIN, H., and ARITAS, R.: *Compt. rend. Soc. d. biol.*, cxxx, 495, quoted from 15.
19. DAVID, N. A.: Uncontrolled use of oral amebicides, *Jr. Am. Med. Assoc.*, 1945, cxxix, 572.
20. ADAMS, A. R. D.: Amebiasis with special reference to treatment, *Trans. Roy. Soc. Trop. Med. and Hyg.*, 1945, xxxviii, 237.
21. NAUSS, R. W., and RAPPAPORT, I.: Studies in amebiasis: I. Pathogenesis of mucosal penetration, *Am. Jr. Trop. Med.*, 1940, xxvi, 107.
22. PAYNE, A. M. M.: Amebic dysentery in Eastern India, *Lancet*, 1945, i, 206.
23. SAPERO, J. J.: Clinical studies in non-dysenteric intestinal amebiasis, *Am. Jr. Trop. Med.*, 1939, xix, 497.
24. LOWE, J., Professor of Tropical Medicine, School of Tropical Medicine, Calcutta: Personal Communication.

ACUTE PERICARDITIS: A STUDY OF EIGHTEEN CASES AMONG SERVICE PERSONNEL *

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PERICARDITIS in itself may be serious or unimportant, or it may be merely an incident in other serious and often fatal diseases. It is often masked by the underlying illness and not thought of until discovered in the course of a physical or roentgenologic examination.

Acute pericardial disease may be classified into three main types: acute fibrinous, acute serofibrinous and purulent. Acute rheumatic fever is the most common etiologic factor in the production of the fibrinous and serofibrinous types. In this condition the pericarditis is a part of a pancarditis in which the endocardium and the myocardium are also affected.¹ Other etiologic factors in the production of these same types are influenza,² pneumococcic pneumonia, primary atypical pneumonia³ and tularemia.⁴ Purulent pericarditis is a complication of disease produced elsewhere in the body by pyogenic bacteria and initiated by hematogenous spread or by direct extension. Besides the etiologic factors already mentioned acute myocardial infarction, penetrating wounds of the thorax, uremia, malignant tumors, lupus erythematosus, periarteritis nodosa and undulant fever should be listed. It may follow tonsillectomy and has been reported following operative procedures, including thyroidectomy.⁵ It has been observed in epidemic form.⁶

It has been said that the diagnosis of acute pericarditis is more often missed than made. Smith and Willius^{7, 8, 9} found 373 cases of pericarditis in the course of 8,912 necropsies, an incidence of 4.3 per cent; in 58 per cent of these 373 cases acute pericardial disease was present.

DIAGNOSIS

In the diagnosis of pericarditis, the general symptoms are those of any severe infectious illness. The local symptoms and signs are few but are characteristic when present. Pain, if present, is sharp, intermittent or continuous, and is usually referred to the precordium and left shoulder. It is accentuated by bodily movements, cough and inspiration. The accentuation of pain under these circumstances is helpful in the differential diagnosis from myocardial infarction according to Wolff.⁶

Cough, orthopnea, hoarseness and dysphagia or dyspnea, weakness, faintness and venous congestion may be produced when pericardial effusion

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develops rapidly and causes pressure on the lungs and trachea or cardiac tamponade.

A to-and-fro pericardial friction rub which may be heard within one to a few hours after the onset of pain, when it is present, is diagnostic of pericarditis. It may be loud and is most frequently heard along the left border of the sternum. Willius¹⁰ stated that a rub is heard in less than 20 per cent of cases in which the pericardium is known to have been involved. Many cases of acute pericarditis will be overlooked if the development of this phenomenon is awaited.

The earliest sign of pericardial effusion is found on roentgenologic examination. It consists of a bulging of the heart shadow, just above the cardiophrenic angles. As the serous exudate increases, the cardiac contour is rounded out, and with the patient standing, it may resemble a water bottle. The size of the heart is difficult to determine because the shadow is usually buried in the shadow of the pericardial effusion. The water bottle configuration is not conclusive evidence of pericardial effusion because the same configuration may be produced by acute cardiac dilatation.¹¹ According to Freedman¹² roentgenologic examination is most reliable when it is repeated daily. Any considerable change in the size of the shadow within a short period of time is the best sign of pericardial fluid. As the fluid increases to the point of cardiac tamponade, the contour of the heart shadow approaches that of a "water bottle" flask and the right and left sides appear symmetrical.

Compression of the right auricle and great veins by the fluid in the pericardium may result in high venous pressure and give rise to enlargement of the liver and tenderness on pressure. The progressive blocking of the hepatic veins and inferior vena cava may give rise to ascites with or without edema of the legs. With large pericardial effusions, the minute volume of blood entering the heart and being pumped into the circulation gradually decreases. This decrease results in low blood and pulse pressure, faint heart sounds, tachycardia and paradoxical pulse.

Electrocardiograms are of distinct diagnostic value in pericarditis. The sequence of changes is best illustrated by serial tracings. A tracing suggestive of chronic tuberculous pericarditis may lead one to secure other confirmatory evidence. In acute pericarditis (figure 1A) the most characteristic picture is elevation of the RS-T segment in all three standard leads or in Leads I and II, in Leads II and III, or in Lead I alone. In the early stage the T-waves may be exaggerated and rather sharp, or they may have a dome-shaped summit. The early changes may subside rapidly. In the subacute stage of pericarditis the elevations disappear and the T-waves may be negative (figure 1B). The changes of chronic tuberculous pericarditis are chiefly those observed in chronic constrictive pericarditis (figure 1C) and include low voltage of the QRS complexes in all the standard leads and low voltage or inversion of the T-waves in all standard leads.¹³

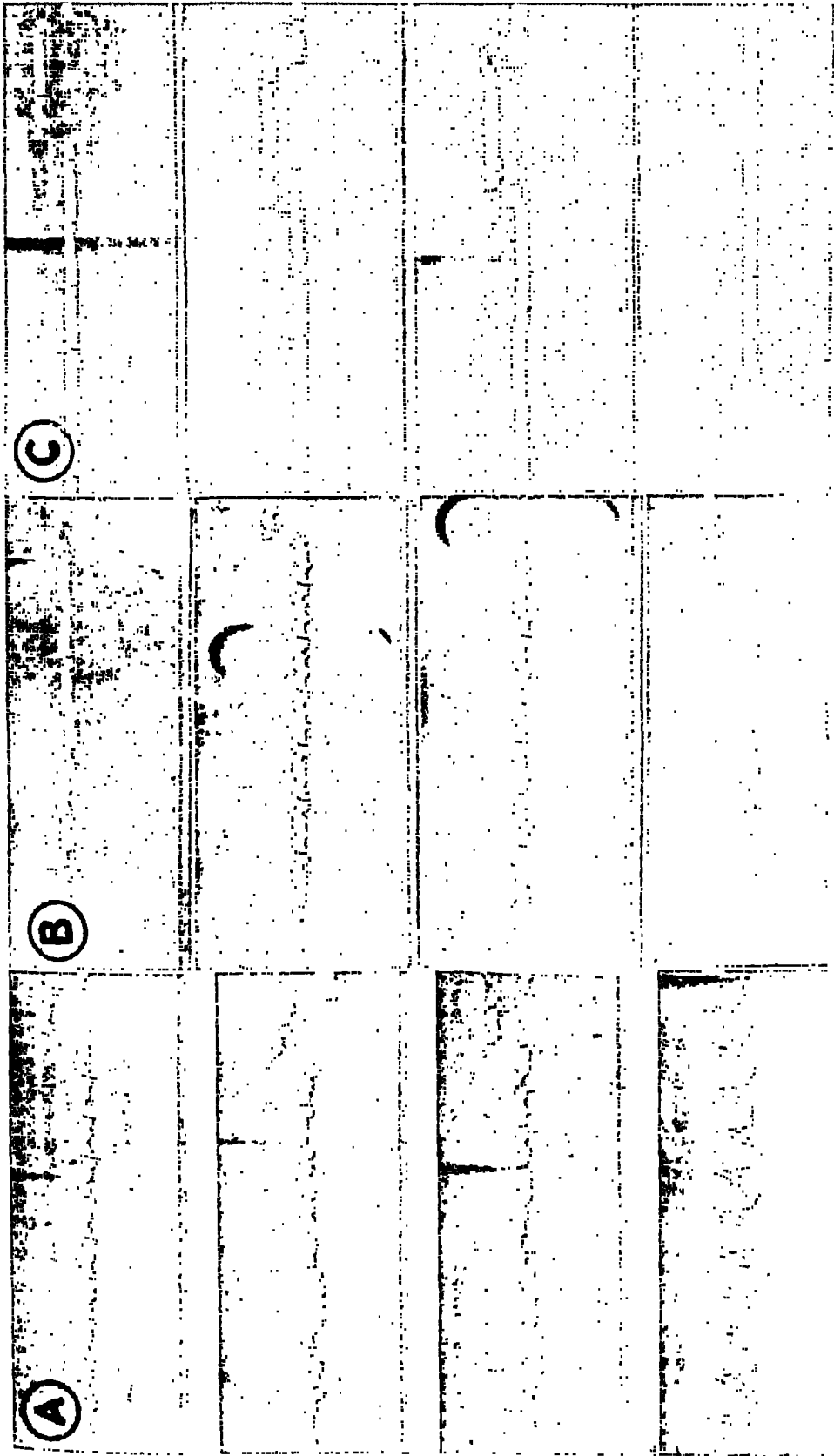


FIG. 1. Electrocardiograms. A. Acute pericarditis in case 1. Elevation of RS-T segment in Leads I, II and IV may be noted. B. Subacute pericarditis in case 2; the T-waves are of low voltage or negative. C. Chronic pericarditis in case 3. Low voltage is noticeable through all leads.

To make the correct diagnosis of pericarditis requires all information that can be obtained by examination of the heart and chest, a complete study of the circulation, radiologic examination, fluoroscopy, electrocardiography and perhaps paracentesis.

In the course of an infection or during a postoperative convalescence, the sudden onset of dyspnea, pain in the thorax with a rapid weak pulse, a drop in blood pressure, chills and fever, and a grayish pallor should suggest pericarditis.

SERIES OF EIGHTEEN CASES

This paper is based on 18 cases of acute pericarditis which were observed in 17 months on a cardiorespiratory service at a United States Naval Hospital.

Eight of the patients were 18 or 19 years of age, eight were in the third decade of life and two in the fourth. All were males; one (case 18) was a Negro (table 1).

TABLE I
The Etiologic Factors, Results and Sick Days in Series of Eighteen Cases

Case	Age, yrs.	Etiologic factor	Result	Sick days
1	18	Rheumatic fever	Died	6
2	21	Bronchopneumonia	Died	28
3	18	Tuberculosis	Transferred	211
4	34	Nonspecific	Duty	100
5	35	Bronchopneumonia	Discharge	172
6	23	Rheumatic fever	Hospital	73
7	21	Nonspecific	Duty	152
8	18	Pharyngitis, rheumatic fever	Hospital	137
9	25	Tracheobronchitis, septicemia	Hospital	287
10	20	Lobar pneumonia, left pleural effusion	Transferred	271
11	18	Atypical pneumonia, right pleural effusion	Hospital	88
12	23	Pharyngitis	Discharge	155
13	18	Pharyngitis	Hospital	185
14	22	Tuberculosis	Hospital	76
15	19	Pharyngitis	Hospital	36
16	18	Rheumatic fever	Died	10
17	19	Rheumatic fever	Transferred	280
18	22	Lobar pneumonia	Died	1

Acute pericardial disease is seen almost exclusively in younger individuals. For that reason, many cases are seen in military service where the majority of personnel are within the age group in which infectious diseases are prevalent.

Various etiologic factors were responsible for the pericarditis in this series (table 1). Rheumatic fever was considered the cause in five cases; pharyngitis in three, pneumonia in five, septicemia in one, tuberculosis in two and in two a nonspecific type of pericarditis was present. These factors are the same as those which have been previously noted in textbooks and reports, but the incidence varied somewhat.

When pericarditis resulted from an infectious disease, the patient was usually seriously ill before the pericarditis developed; it usually developed in from three days to two weeks after the onset of the infection. At times the exact primary infection was difficult to determine. Present symptoms or a past history of symptoms referable to either the joints or the heart were considered to be definitely rheumatic. Episodes of acute pharyngitis, particularly when associated with constitutional reactions of fever and malaise were considered significant. Pneumonia, tuberculosis and septicemia were diagnosed by clinical and laboratory examinations. Two patients did not give a history of any recent infectious process, and their condition was classified as a nonspecific inflammatory pericarditis which is reported as occurring under various circumstances unassociated with the commonly recognized causative factors.

A rub was heard during some stage of the illness in 14 of the 18 patients in this series.

In this group of 18 cases two men were cured (table 1). (The term "cured" is used in a restricted sense to mean "had no symptoms or signs present from three to five months after the onset of their illness.") Two were discharged from the service after six months in the hospital, because of residual changes. Ten continued to receive hospitalization because of recent onset, or the presence of valvular heart disease, empyema or effusion under treatment. One of these (case 3) is known to have died after being transferred to another hospital. Four men died in the hospital, two from pneumonia and purulent pericarditis, and two from rheumatic pancarditis with pericarditis. Both of the latter had had a previous attack of rheumatic heart disease not diagnosed clinically. The sick days of these 18 men had varied from one to 287 at the time of writing this paper.

Three representative cases are reported in detail.

CASE REPORTS

Case 1. A sailor, aged 18 years, was admitted to the hospital because of swelling and severe pain in his joints of three days' duration and pain in his left thorax for one day. He had been told that he had rheumatic fever five months previously. At that time he had been playing football and noted pain in both legs which was not disabling and did not require medical treatment. Thereafter he had felt well until his present illness. The articular pain began in his right elbow and was associated with swelling. After two days, the pain and swelling spread and involved his left wrist. The day before admission his knees and ankles were so painful that he was unable to walk. Concurrently a sharp, almost continuous pain developed over his heart. This pain was worse on inspiration so that he breathed with difficulty.

The patient weighed 197 pounds (89.4 kg.) and was well developed. He appeared acutely and seriously ill. His temperature was 100° F.; the pulse rate was 132 beats per minute and blood pressure was 90 mm. Hg systolic and 70 mm. diastolic. The respiratory rate was 28 per minute and breathing was shallow and labored. Fine crackling râles were heard at the bases of both lungs. Palpation revealed friction fremitus over the precordium, and a loud grating pericardial friction rub was heard in that region. The heart was enlarged to the right and left. Both systolic and diastolic murmurs were heard in the region of the mitral valve. Tenderness was

noted in the upper part of the abdomen. His ankles, knees and left wrist were red and swollen and so painful that light pressure on these parts caused him to cry out.

Laboratory data on, or shortly after, admission included a negative blood culture and a negative Kahn reaction on the blood. The value for hemoglobin was 71 per cent; erythrocytes numbered 3,310,000 per cubic millimeter with an occasional nucleated cell, and leukocytes numbered 5,850 per cubic millimeter. The differential count revealed polymorphonuclear cells 95 per cent, lymphocytes 4 per cent and monocytes 1 per cent. The value of blood chlorides in milligrams per 100 c.c. was 360, and of serum proteins in grams per 100 c.c. 68. A bedside roentgenogram of the chest revealed a hazy mottled increase in density in the lower part of both lungs (figure 2). The transverse diameter of the heart was 19.6 cm. and of the chest 31.5 cm. Because the roentgenogram was made at the bedside, the size of the heart could not be accurately determined, but it took up more than 50 per cent of the transverse diameter of the chest and was enlarged to the right and left. An electrocardiogram revealed upward displacement of the RS-T segments in Leads I, II and IV. The T-wave in Lead III was inverted (figure 1A).

A diagnosis of rheumatic heart disease with pericarditis was made.

The patient was placed in an oxygen tent and given sedatives and large doses of sodium salicylate. On the second day in the hospital his temperature rose to 103.2° F., and the pulse rate continued to be rapid. Respirations were shallow and labored, and he continued to have pain in the left side of the chest. There was no change in the

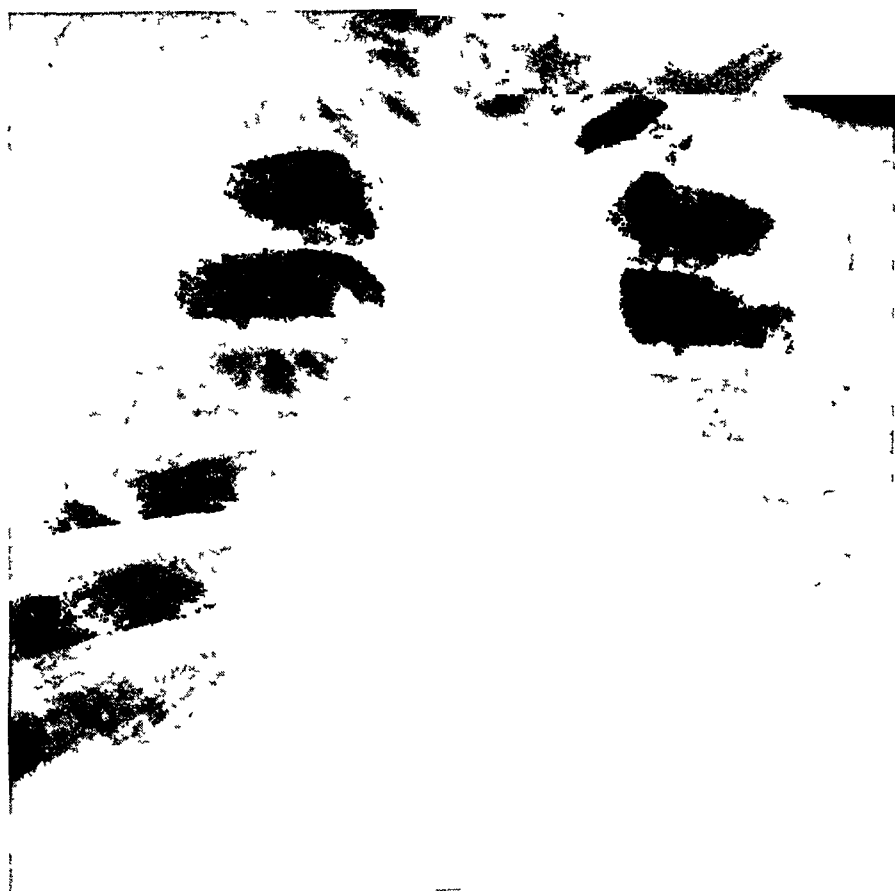


FIG 2 (case 1). Heart is enlarged to the right and left. Contour of the heart should be noted.

intensity of the pericardial rub. Sulfadiazine was administered in adequate doses, and on the third day in the hospital the temperature became normal. However, dyspnea continued and the patient was slightly confused. The liver became palpable and tender. There was no change in the heart. Digitalization with cedilanid was carried out rapidly, and administration of this drug was continued parenterally.

On the fourth day in the hospital the patient exhibited a grayish pallor. Temperature was 101° F. Signs of congestion in both lungs increased, but the condition of the heart and the pericardial rub continued as before. Administration of penicillin in adequate dosage was begun, but the temperature continued to rise and was 102.6° F. on the fifth day. The patient became more dyspneic and the temperature continued to rise. He did not respond to treatment and died.

Postmortem examination revealed rheumatic pancarditis with acute fibrinous pericarditis. The heart was dilated and hypertrophied and covered with a yellow-gray shaggy fibrinous exudate. On opening the heart the mitral valve was thickened and the adjacent edges of the leaflets fused. The free border was rolled and studded with verrucous vegetations. Fine granular vegetations were seen on the cusps of the aortic valve. The attached chordae tendineae were thickened. The myocardium showed small foci of infiltration and an occasional Aschoff cell. There was no fibrosis. A small amount of fluid was found in each pleural cavity. There was passive congestion of the liver.

Acute pericardial disease as a complication of rheumatic fever may subside spontaneously. However, Holt¹¹ reported on the gravity of pericarditis in rheumatic fever. Acute pericarditis was the turning point in the disease for 26 of her patients, only one of whom was known to be alive three years after the attack. In our experience, pericarditis may be a concurrent sign and symptom of a rheumatic pancarditis.

Case 2. The patient, aged 21 years, was admitted to the hospital because of pain in the left side of the thorax. He had had pneumonia at the age of one year and sinus trouble for about four years. A severe attack of the latter had occurred one year before admission, and irrigation of the sinuses was performed about one week before. Otherwise, his general health had been good until the onset of his present illness. Five days prior to admission he first noticed malaise and anorexia and experienced nausea and vomiting on two occasions when he attempted to eat. Two days before admission he had epistaxis. The same day he had a shaking chill followed by fever and pain in the left side of the chest, and he coughed up some yellow sputum. The pain was aggravated by respiration.

On examination dyspnea and cyanosis of the fingernails were noted. The patient was restless, apprehensive, and appeared seriously ill. The temperature was 102.8° F.; the pulse rate was 120 beats per minute and blood pressure was 112 mm. Hg systolic and 60 mm. diastolic. Respiratory rate was 32 per minute and respiration was shallow and labored, but there was equal movement on both sides. The mouth was dry. The heart was enlarged to the right and left. There were no murmurs. On percussion there was dullness in the base of the left lung and tubular breathing; crackling râles were heard in the same region.

A trace of albuminuria was found. Gram stain of the sputum revealed many gram-positive cocci in clusters and pairs. The value for hemoglobin was 84 per cent, the erythrocyte count was 3,940,000 per cubic millimeter, and the leukocyte count, 12,050. The differential count revealed polymorphonuclear cells 76 per cent, lymphocytes 21 per cent, and monocytes 3 per cent. In the bedside roentgenogram of the chest (figure 3A) the transverse diameter of the heart was 20.8 cm. and that of the chest was 29.5 cm.

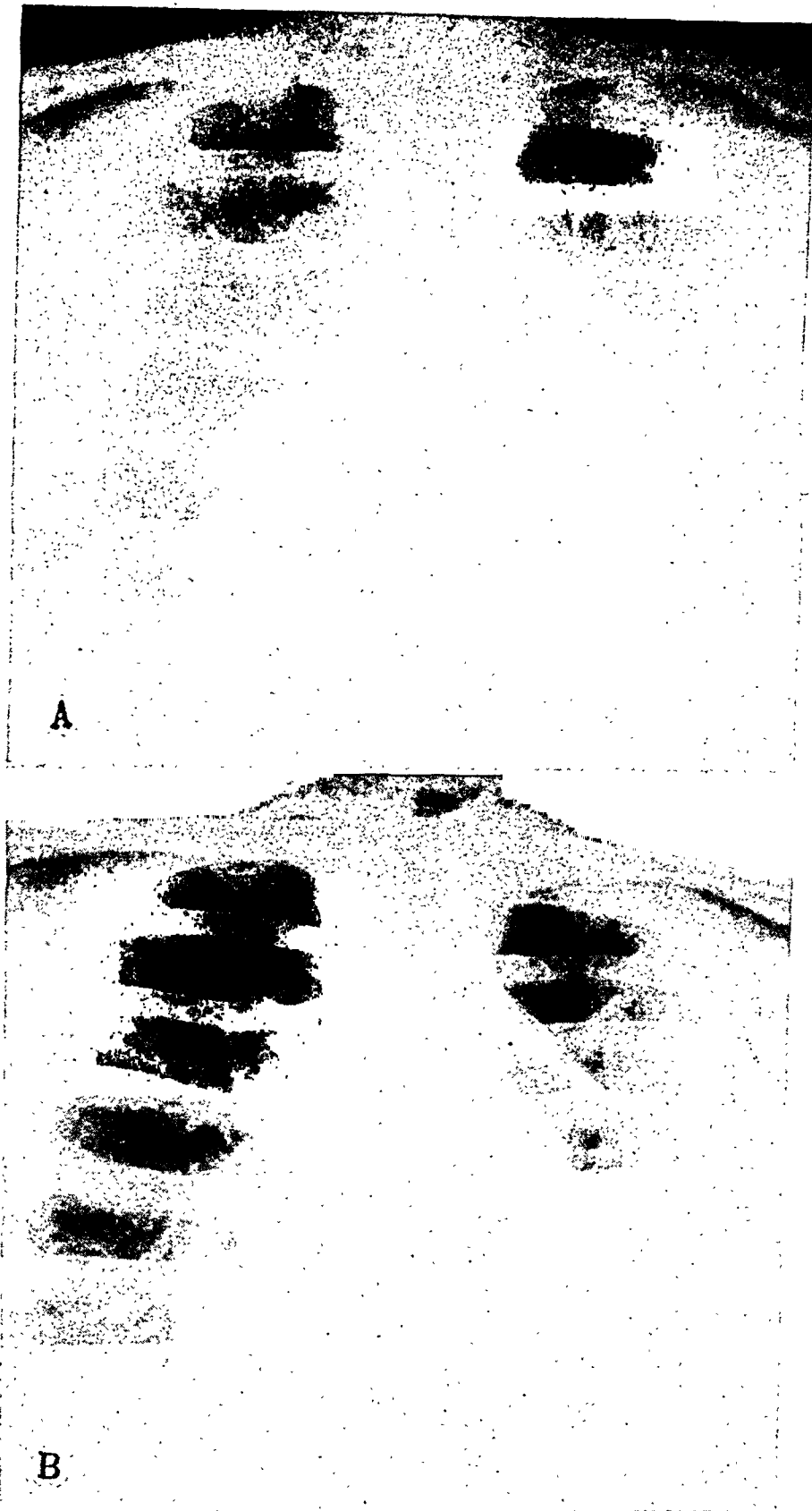


FIG. 3 (case 2). *A*. Heart is enlarged to the left and right. *B*. Actual size of the heart is indicated. View made after withdrawal of fluid from and injection of air into the pericardial sac.

A diagnosis of bronchopneumonia with pericarditis was made.

The patient was placed in an oxygen tent and given sedatives. Intravenous administration of penicillin was begun at once with 100,000 Oxford units in 5 per cent solution of glucose and thereafter 15,000 units were given every three hours. Also 1 gm. of sulfadiazine and 10 grains (0.65 gm.) of sodium bicarbonate were prescribed every four hours. By the third day in the hospital the patient's color was improved. The liver was enlarged about three fingers' breadth below the right costal margin and was tender. Crackling râles were still present in the left lung.

The following day the pulse became weak and the rate rose to 120 beats per minute. The heart tones were distant and muffled. On the fifth day in the hospital the patient was restless and dyspneic. The pulse was paradoxical. Pericardial paracentesis was done and 90 c.c. of cloudy yellow fluid with coagulum were aspirated. The temperature became normal that day.

The next day the patient again was dyspneic and uncomfortable. He could not eat and could drink little. The paradoxical pulse was weak. Blood pressure was 100 mm. Hg systolic and 60 mm. diastolic. The temperature was 101° F. The patient breathed more easily after 450 c.c. of cloudy yellow fluid were removed and 20,000 Oxford units of penicillin were instilled into the pericardial cavity. The blood pressure rose to 140 mm. Hg systolic and 90 mm. diastolic; the pulse became stronger and was no longer paradoxical. Examination of the purulent fluid, including a smear for tubercle bacilli, revealed no organisms, and the culture was negative. A guinea pig was inoculated with the fluid with negative results. Studies made on other occasions were also negative, and the differential cell counts made revealed from 79 to 96 per cent polymorphonuclear leukocytes.

The patient's abdomen became tender and distended. The administration of sulfadiazine was discontinued, and local application of heat, enemas and intramuscular injections of methylsulfate (prostigmine) were given with little relief. Profuse diaphoresis, precordial pain and dyspnea were present. Dullness and a pleural friction rub were noted in the base of the left lung. On the seventh day in the hospital 370 c.c. of cloudy yellow fluid with a bloody pellicle were removed from the pericardial cavity, and 35,000 Oxford units of penicillin were instilled into it. A harsh grating pericardial friction rub was heard. The pericardial shadow was slightly decreased on roentgenologic examination. The temperature continued to be elevated and the record was of a spiking nature, especially in the evening. Adequate fluids were given orally and intravenously. Oxygen was used as needed. Respiration seemed less labored.

On the ninth day in the hospital dyspnea and restlessness were noticeable. At this time 585 c.c. of clear yellow fluid were withdrawn, and 100,000 Oxford units of penicillin and 150 c.c. of air were injected into the pericardial cavity.

Another bedside roentgenogram (figure 3B) following instillation of air into the pericardial sac revealed a greatly thickened pericardium, a large amount of fibrinous exudate which partially obscured the border of the heart and evidence of pneumonitis in the left lower lobe. The patient seemed improved and did not complain of shortness of breath. He was coughing a little and râles were heard in both sides of his chest. He continued to have fever as high as 102° F. Two successive blood cultures were negative.

On the fourteenth day in the hospital the patient complained of pain in the right side of the chest and a pleural friction rub was heard in that area. He again noted some shortness of breath for which he requested oxygen. The pericardial rub, previously heard, disappeared. Removal of 375 c.c. of yellow fluid made a total of 1,870 c.c. removed from the pericardial cavity, and 100,000 Oxford units of penicillin and 250 c.c. of air were instilled into the pericardial sac. The temperature had slightly decreased to 101° F. An electrocardiogram revealed low voltage of the

T-wave in Lead I and inversion of the T-waves in Leads II, III and IV. These findings were suggestive of subacute pericarditis (figure 1B). The patient again seemed improved and took an interest in things about him. Oxygen therapy was discontinued. He continued to have upper abdominal soreness; his temperature was 100° F., and his heart rate was 100 to 110 beats per minute.

On the twenty-second day in the hospital the patient again complained of shortness of breath, nausea and abdominal soreness. He began to cough up bright red blood. The heart sounds were distant, the pulse rate was 110 beats per minute, and the pulse was weak and thready. Râles were still present at the bases of both lungs. The abdomen revealed some shifting dullness. Digitalization was carried out rapidly by oral and intramuscular routes for two days and doses of this drug were given thereafter. Fluids were limited and diuresis was attempted. On the twenty-eighth day in the hospital respiration became labored and cyanosis appeared; the patient went into shock and died.

Postmortem examination revealed interstitial pneumonitis, extensive fibrinous pericarditis, toxic hepatitis, pulmonary hemorrhagic infarcts, and bilateral hydrothorax and ascites. The pericardial sac was adherent to the mediastinum and the adjacent surfaces of the lungs. The parietal pericardium was from 3 to 5 mm. thick. The epicardium and the pericardium were covered with a thick shaggy layer of fibrin and were partly adherent to each other. Free fluid was present in the spaces not obliterated by the adhesions. A roll of fibrin 9 by 5 by 3.5 cm. was lying along the left border of the heart. The myocardium was pale and soft. No changes were seen in the endocardium.

This case is representative of the occasional case of serious purulent pericarditis secondary to disease elsewhere in the body which is often fatal. Wise and Shafer¹⁵ recently reported a case of purulent pericarditis cured by the intrapericardial injection of 40,000 Oxford units of penicillin. Our patient received a total of 3,840,000 Oxford units of penicillin parenterally during his illness and 255,000 units intrapericardially. The acute mediastinopericarditis seen in this case resembles that seen in chronic constrictive pericarditis.

Case 3. The patient, aged 18 years, was admitted to the hospital after he had fainted at muster. He had been well until two years before, when he had had intermittent fever for several months. The next year he had had a recurrence of the fever. Nine months before admission he was treated for measles and seven months before admission he had catarrhal fever. He had convalesced slowly from this, had continued to feel weak and had not regained his usual strength. His mother had died from tuberculosis when he was eight years of age.

In the hospital the temperature, pulse and respiration were normal and the patient gained weight. Repeated roentgenograms of the chest revealed mild fibrosis in the right medial portion of the lungs, extending upward from the hilum toward the clavicle (figure 4A). The fibrosis remained unchanged during the entire period of observation (figure 4B). Some cardiac enlargement was noted; but the ratio of the diameter of the heart to that of the thorax was 47 per cent and within normal limits. Repeated examinations of the sputum and concentrates of gastric washings were negative for tubercle bacilli.

The patient returned to duty feeling well after 118 days in the hospital. One week later, however, he noticed some shortness of breath. The morning of admission he complained of pain in the chest and had more severe dyspnea.

On examination dyspnea and cyanosis of the lips and fingernails were noted. The patient was restless and apprehensive and appeared extremely ill. Temperature was

102.6° F.; pulse rate was 104 beats per minute, and he had a paradoxical pulse. The blood pressure was 118 mm. Hg systolic and 88 mm. diastolic. The veins of the neck were distended. Cardiac dullness extended 5 cm. to the right of the sternum and to the left midaxillary line. The heart sounds were distant. No murmurs were heard. A pericardial rub was heard to the left of the lower portion of the sternum. The abdomen was slightly distended, and the liver was enlarged and tender. The remainder of the examination revealed no significant findings.

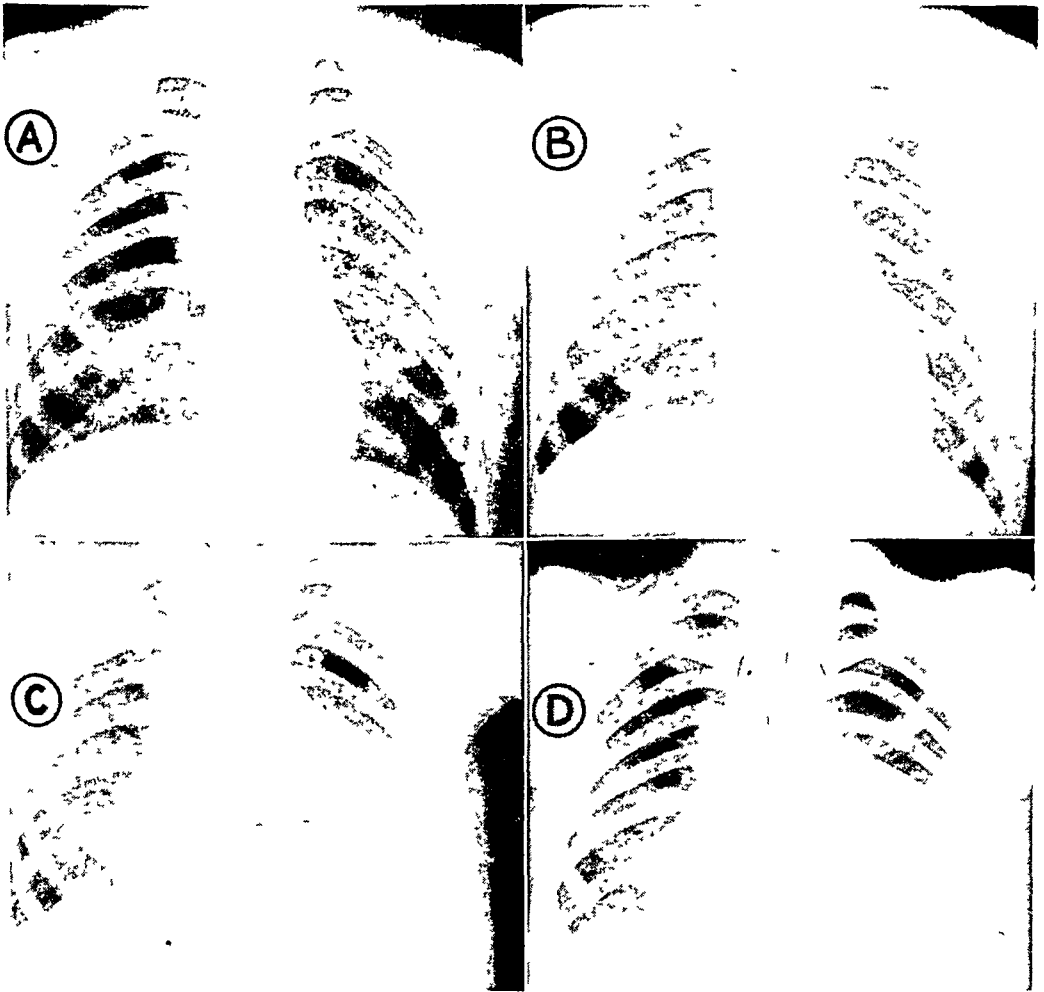


FIG. 4 (case 3). Gradual development of pericardial effusion which is typical of tuberculous pericarditis. A. April 28, 1944. B. August 18, 1944. C. September 6, 1944. D. November 2, 1944.

Laboratory studies revealed a value for hemoglobin of 65 per cent (Haden-Hauser test) and 3,400,000 erythrocytes and 4,450 leukocytes per cubic millimeter of blood. On differential count, 78 per cent of the leukocytes were polymorphonuclear cells, 20 per cent were lymphocytes and 2 per cent were eosinophiles. Moderate albuminuria was present. A bedside roentgenogram of the chest revealed the rather marked cardiac enlargement noted clinically (figure 4C), and a water bottle-like configuration. The transverse diameter of the heart measured 21.8 cm. and that of the chest was 30.5 cm. An electrocardiogram demonstrated tachycardia of sinus origin, and T-wave negativity in Leads I, II, III and IV.

The diagnosis was pericarditis with effusion, possibly tuberculous in origin.

The pericardium was at once aspirated and 400 c.c. of serosanguineous fluid were removed. This procedure gave relief. Examination of the fluid revealed five leukocytes per cubic millimeter; no organisms were seen on smear, and the culture was negative. The respiratory rate slowed and the paradoxical pulse disappeared. The patient was placed in an oxygen tent and treatment with penicillin was begun. Shortness of breath, precordial oppression and a weak rapid pulse were present again on the second day. A second aspiration yielded 450 c.c. of transudate. The arterial pressure increased to 130 mm. Hg systolic and 86 mm. diastolic, and the dyspnea decreased. Examination of the fluid was again negative as was guinea pig inoculation. Gradually signs of cardiac tamponade returned and the pericardial rub disappeared.

On the seventh day in the hospital a third aspiration of the pericardium was performed, again, with relief of dyspnea and precordial oppression. Smear, culture and guinea pig inoculation again revealed nothing abnormal. Fever continued and the record of the afternoon temperature was spiking in contour. Blood cultures were negative. After twelve days of treatment with penicillin during which a total of 2,880,000 Oxford units had been given, its use was discontinued and sulfadiazine was given in the dosage of 5 and later 4 gm. daily. This treatment too was discontinued when the course of the disease and fever continued. Supportive treatment in the form of rest, high caloric diet, blood transfusions, multivitamins and ferrous sulfate was initiated.

About three weeks after admission, fluid began to form in the left side of the thorax and rose to the level of the second interspace anteriorly. Five weeks after admission, left thoracentesis was done and 1,000 c.c. of serosanguineous fluid were removed. The patient continued to have moderate shortness of breath, and two weeks after the first thoracentesis the left side of the chest was again aspirated and 850 c.c. of yellow fluid removed. The patient felt improved. Another roentgenogram of the chest revealed a definite fluid level at the lower edge of the tip of the third rib anteriorly (figure 4D). An irregular band ran outward and upward from the right hilum. Ten days later a third aspiration was performed and 1,800 c.c. of serosanguineous fluid were removed from the left side of the thorax.

Gradually the patient became weak, listless and sallow. He had anorexia, epigastric distress and lost weight. Dyspnea was marked on exertion and was relieved by rest. He produced about one teaspoonful (4 c.c.) of yellow sputum daily and repeated examinations for tubercle bacilli were negative. Daily low-grade fever and spiking records of the evening temperature continued.

About 10 weeks after admission the abdomen gradually became distended and shifting dullness was present. Edema of the extremities developed. The patient was slowly digitalized, intake of fluids and salt was limited, and acid salts and mercurial diuretics were used with fair results. Three months after admission, abdominal paracentesis was performed and 1,020 c.c. of cloudy straw-colored fluid were removed. The patient became progressively worse. He had more shortness of breath, and fluid rapidly accumulated in the body cavities, except in the right side of the chest, and in the soft tissues. An electrocardiogram (figure 1C) revealed QRS complexes and T-waves of low voltage, which was suggestive of chronic pericarditis.

The patient had a characteristic attitude of distress, sitting upright in bed and leaning far forward. His venous pressure was 40 cm. of water. In order to prevent mechanical embarrassment of the heart by the accumulation of too much effusion, a fourth aspiration of the pericardium was done and 600 c.c. of fluid were removed, with relief to the patient. Guinea pig inoculation for the first time revealed tubercle bacilli. Abdominal paracenteses were performed as needed for relief of the distention. Owing to the recurring ascites, consultation with a thoracic surgeon was requested but it was decided that, in view of the persistent fever despite rest in bed and in view

of the activity of the infection, treatment should continue to be symptomatic and supportive. About five months after admission, a stained smear of the abdominal fluid revealed tubercle bacilli for the first time.

Gradually the patient began to feel somewhat improved and wished to be transferred to a hospital near home, and this was done. However, he continued to lose weight, and one day became irrational and developed signs of meningeal irritation.

The spinal fluid contained many leukocytes and the predominating cells were lymphocytes. He failed to improve and died.

Postmortem examination revealed tuberculous pericarditis, nodular tuberculosis of the tracheobronchial lymph nodes, localized lymphogenous miliary tuberculosis of the apex of the upper lobe of the right lung, acute tuberculous leptomeningitis, tuberculous ulcers of the ileum with involvement of the mesenteric lymph nodes, bilateral hydrothorax, ascites and edema of the legs.

Several large, soft, caseous tracheobronchial lymph nodes were matted with partial fixation of mediastinal structures near the superior portion of the pericardial sac. The pericardial surfaces were thick, shaggy, soft and pale yellow-green with only small ill-defined collections of free fluid. The heart had an estimated weight of 350 gm. without the pericardium, the visceral layer of which was 1 cm. in average thickness, including the shaggy exudate. Tubercles were seen near the myocardium in sections from the heart. No alterations were seen in any of the valves or in the deep myocardium.

The history of the insidious onset of the symptoms and the absence of pain suggested tuberculosis in this case, although the patient's contact with tuberculosis had occurred in the remote past. The development of large quantities of effusion over rather long periods of time is characteristic. The tuberculous origin in this case was proved when guinea pig inoculation with the pericardial fluid revealed tubercle bacilli, although repeated inoculations were necessary before the diagnosis was confirmed.

COMMENT

When the characteristic electrocardiographic pattern of acute pericarditis occurs, diffuse subepicardial myocarditis is present according to Burchell, Barnes and Mann.¹⁶ When this process undergoes resolution and repair only slight thickening of the pericardium may remain, or with deeper and more extensive inflammation, adhesions between the layers of the pericardium and surrounding structures may result. The duration of acute pericarditis may vary from a few days to a few weeks, and it may recur¹¹ or chronic pericarditis may result, which may produce symptoms and signs after the lapse of some months or years.

The etiology of chronic constrictive pericarditis is of considerable interest and importance. Harrington¹⁷ reported on five of 24 patients treated surgically for this condition. The clinical history and examination in these five cases, and microscopic study and culture made of the tissue removed at operation proved that the etiologic agent was tuberculosis. In the remaining 19 cases the type of primary infection was unknown. Eight of these 19 patients gave a history of one or more previous attacks of some pulmonary infection as pneumonia or influenza. Nine did not give a history

of any infectious process to which the condition could be attributed. These findings are in line with those reported by other workers.¹⁸ In a follow-up study of 37 cases of constrictive pericarditis seen at the Massachusetts General Hospital, Harrison and White³ reported that rheumatic fever is rarely, if ever, an etiologic factor.

Future observation of the patients who survived the episode of acute pericarditis would be most interesting for, as Broadbent¹⁹ pointed out in 1895, "the key to the solution of adherent pericardium lies in watching cases of acute pericarditis as they go on to the formation of adhesions."

BIBLIOGRAPHY

1. WHITE, P. D.: Heart disease, Ed. 2, 1937, The Macmillan Company, New York, pp. 461-468.
2. KRESKY, P. J.: Suppurative pericarditis due to *Haemophilus influenzae* type B; a characteristic syndrome ushered in by symptoms of croup, Am. Jr. Dis. Child., 1943, lxx, 305-313.
3. HARRISON, M. B., and WHITE, P. D.: Chronic constrictive pericarditis; a follow-up study of 37 cases, Ann. Int. Med., 1942, xvii, 790-806.
4. JAGER, B. V., and RANSMEIER, J. C.: Constrictive pericarditis due to *Bacterium tularense*; report of a case and review of reported cases of pericarditis occurring with tularemia, Bull. Johns Hopkins Hosp., 1943, lxxii, 166-178.
5. SPEAR, P. W.: Fibrinous pericarditis following thyroidectomy, South. Med. Jr., 1938, xxxi, 215-218.
6. WOLFF, LOUIS: Acute pericarditis simulating myocardial infarction, New England Jr. Med., 1944, ccxxx, 422-425.
7. SMITH, H. L., and WILLIUS, F. A.: Pericarditis. I. Chronic adherent pericarditis, Arch. Int. Med., 1932, 1, 171-183.
8. SMITH, H. L., and WILLIUS, F. A.: Pericarditis. II. Calcification of pericardium, Arch. Int. Med., 1932, 1, 184-191.
9. SMITH, H. L., and WILLIUS, F. A.: Pericarditis. III. Pericarditis with effusion, Arch. Int. Med., 1932, 1, 192-202.
10. WILLIUS, F. A.: Cardiac clinics, 1941, St. Louis, C. V. Mosby Company, p. 30.
11. WOLFF, LOUIS: Acute pericarditis with special reference to changes in heart size, New England Jr. Med., 1943, ccxxix, 423-431.
12. FREEDMAN, EUGENE: Inflammatory diseases of the pericardium, Am. Jr. Roentgenol., 1939, xlii, 38-46.
13. NOTH, P. H., and BARNES, A. R.: Electrocardiographic changes associated with pericarditis, Arch. Int. Med., 1940, lxx, 291-320.
14. HOLT, EVELYN: Chronic adhesive pericarditis in childhood, Am. Jr. Med. Sci., 1929, clxxviii, 615-631.
15. WISE, A. W., and SHAFER, L. E.: Purulent pericardial effusion treated with penicillin given intrapericardially, Jr. Am. Med. Assoc., 1945, cxxvii, 583.
16. BURCHELL, H. B., BARNES, A. R., and MANN, F. C.: Electrocardiographic picture of experimental localized pericarditis, Am. Heart Jr., 1939, xviii, 133-144.
17. HARRINGTON, S. W.: Chronic constrictive pericarditis: partial pericardiectomy and epicardiolysis in 24 cases, Ann. Surg., 1944, cxx, 468-487.
18. SPRAGUE, H. B., and WHITE, P. D.: The indications for and results of pericardial resections—the course of five cases, Med. Clin. N. Am., 1932, xv, 909-917.
19. BROADBENT, J. F. H.: Adherent pericardium, 1895, Baillière, Tindall & Cox, London, 126 pp.

TREATMENT OF HYPERTHYROIDISM WITH PROPYLTHIOURACIL *

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THE current differences of opinion regarding the best form of treatment for hyperthyroidism are a reflection of the fact that of the several effective methods which are available, none is devoid of significant disadvantages. Experience with the use of antithyroid compounds is sufficient to show that this is a highly effective form of treatment, but extensive clinical trials have been carried out only with one such drug, thiouracil. The disadvantage attending the use of this compound relates almost exclusively to its side effects,¹ the drug fever syndrome or some variant of it and agranulocytosis. The former reaction usually precludes the continued use of the drug; the latter is of such severity as sometimes to cause death. These reactions together with milder ones less certainly related to the medication have been encountered in about one of every 10 patients treated with thiouracil.

With the aim of finding more satisfactory agents for clinical use many hundred compounds have been tested in animals. To date, the most active substance encountered has been propylthiouracil, and it has therefore been investigated in human beings.

This study is mainly concerned with the dosage of propylthiouracil in relation to the rate and to the degree of the metabolic response and with the incidence of untoward side effects. Other important considerations such as the general applicability of antithyroid drugs to the treatment of hyperthyroidism, the proper duration of treatment, the incidence of lasting remissions, and the effects of treatment on the condition of the eyes and of the thyroid gland are common to this and to other effective antithyroid compounds. As they do not bear specifically on this particular agent they will not be considered in detail here.

CLINICAL MATERIAL

This report is based upon observations on the first series of 100 cases to be treated with propylthiouracil. These cases were unselected, and the series comprises all cases of hyperthyroidism encountered during the 12 month period from April 1945, to April 1946. Preliminary data on the first 37 of these have already been published.² The 100 cases were made up of 80

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Propylthiouracil was supplied by Dr. S. M. Hardy of the Lederle Laboratories, Inc., Pearl River, New York.

women and 20 men, 21 to 76 years of age. Fifty-seven had not previously received any form of therapy for hyperthyroidism, implying that these were either early cases or ones which had not been diagnosed formerly. Forty-three had been treated in the past either by operation, by iodine, by other antithyroid drugs, or by more than one of these methods. Subtotal thyroidectomy had been performed in 10 instances, two of which had had multiple operations. A total of 29 cases had at some time received iodine, and 21 of these had had iodine up to less than one month prior to the initiation of propylthiouracil therapy. Fifteen patients had had other antithyroid drugs, three of them more than one such drug. Of the seven instances of previous thiouracil medication, significant toxic manifestations had been noted in five; thiobarbital had been given to four patients, two of whom reacted unfavorably to it; ethylthiouracil had been used in seven instances without untoward effect.

Associated disorders and complications of hyperthyroidism were numerous. Thyrotoxic heart disease was diagnosed in 10 patients, five of whom had auricular fibrillation. Heart failure was considered to be due to rheumatic heart disease in three other persons. Three patients became pregnant and delivered normal children during the course of therapy. Other complications and associated disorders were: thyrotoxic myopathy, rheumatoid arthritis, diabetes mellitus, the menopause, obesity, cirrhosis of the liver or impaired liver function, peptic ulcer, pulmonary tuberculosis, thrombophlebitis, cholelithiasis, pernicious anemia, myasthenia gravis, spinal cord tumor, psychoneurosis and manic-depressive psychosis.

THERAPEUTIC PROCEDURE

With few exceptions, treatment was carried out without bed rest or significant restriction of activity. The exceptions were patients with heart failure and one with thyrotoxic myopathy who required rest. These and a few patients on whom special studies were being made were kept in the hospital for the first few weeks of treatment. Propylthiouracil was administered by mouth in the form of 25 mg. tablets at intervals of 8 or 12 hours. The initial dose was usually continued until all symptoms and signs of hyperthyroidism had disappeared. If, after a number of weeks, the rate of response was thought to be unduly slow, the dosage was increased and continued at the higher level until metabolic equilibrium was restored. Not until the patient had regained normal health was the dose reduced except in a few instances to be mentioned below. The maintenance doses were then continued for a minimum of six months. This arbitrary period of six months of normal health is probably a better estimate of the proper duration of treatment than one based upon the total period of therapy.

When propylthiouracil was being given other specific treatment was seldom used. When iodine had previously been given it was discontinued abruptly in most instances, but in severe cases it was gradually withdrawn

during the week or 10 days after propylthiouracil had been started. In two instances iodine in small doses was given for short periods during propylthiouracil therapy. These were cases with large vascular thyroid glands which exhibited further enlargement and increased vascularity during treatment. It should be noted these were the only cases in the series which experienced any significant thyroid enlargement during or after treatment. The only other therapy used was that prescribed for associated disorders such as heart failure, menopausal symptoms, etc.

No special diet or dietary supplements were provided, and none of the several agents which have been claimed to reduce the incidence of drug toxicity were employed. Frequent leukocyte counts were made only during the earlier part of the study. After some 50 patients had taken the drug without apparent harm, subsequent patients were not warned of any dangers associated with drug therapy. They were usually seen in the clinic or by their private physicians every few weeks until the hyperthyroidism was controlled and then at two to three month intervals thereafter.

Incidental to the study of this compound it has been found that the progress of the hyperthyroidism and the effects of treatment can be as well observed by the use of clinical criteria as by the frequent determination of the basal metabolic rate or the use of other special laboratory procedures. The dose can be properly adjusted on the basis of symptoms and such simple signs as the general appearance and behavior of the patient, the body weight, the pulse rate, the forcefulness of the heart beat, the condition of the skin, the steadiness of the hands and the size and vascularity of the thyroid gland. Excessive dosage is suggested by lethargy, sluggishness, an excessive gain in weight, a pasty and puffy appearance to the face and a conspicuous enlargement of the thyroid gland.

DOSAGE AND RESPONSE

The earlier portion of this study was mainly concerned with a determination of the minimal effective dose. As a consequence, many patients received doses which later on were regarded as inadequate. A deliberate attempt was made to avoid excessive doses, and with few exceptions this aim was achieved. The majority of the first 70 cases received as an initial dose 25 mg. every eight hours. In one quarter of these the quantity was subsequently increased to 100 or 150 mg. daily. It was evident that, on the average, the rate of response to 75 mg. daily was slower than the rate of improvement with thiouracil in doses of 0.4 to 0.6 gm. daily. Also, it became clear that certain cases failed to be completely controlled by this dose even when it was continued for as long as five months. The majority of the last 30 cases included in this report received 100 or 150 mg. daily as an initial dose. The rate and degree of the response was significantly more satisfactory in this group.

An estimate of the minimal effective dose may be inferred from the data

shown in figure 1. In the upper diagram is shown the distribution of the initial doses employed in these 100 cases, while the lower diagram shows the maximal doses found necessary to restore metabolic equilibrium. The data reveal a considerable individual variation in dosage requirement. Fifty-seven per cent of the patients were eventually completely controlled by daily doses of 75 mg. or less, while in the remaining 43 per cent doses of 100 or 150 mg. were given initially or were found to be necessary later on in order to restore metabolic equilibrium.

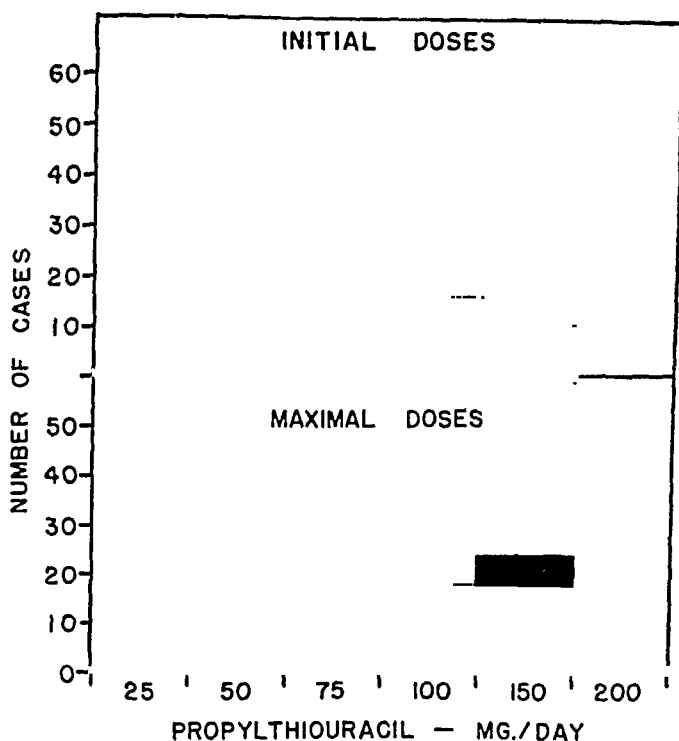


FIG. 1. The *upper diagram* shows the actual initial dosage used in the 100 cases. It varied from 25 to 200 mg. daily, but the majority of cases received 75 mg. The *lower diagram* shows the maximal dosage used during the entire period of treatment. A comparison of the two charts indicates that the arbitrary starting doses frequently had to be increased.

These findings, while pointing to the minimal doses which can be employed, do not provide a clear definition of the optimal dose for routine use. At present there is no method of determining in advance whether a given case will require a small or a large dose. An analysis of the individual patients summarized in figure 1 suggests that those requiring the larger doses were the more severe and more long-standing cases, those with large nodular glands and those who had taken prolonged courses of iodine. These criteria are not sufficiently reliable, however, to permit one to gauge the dose in all instances. It would be desirable to know the dose which would control all cases in a minimal period of time. This doubtless would be a larger dose than has been employed in this study, and one could safely predict that

its continued use would result in a troublesomely high incidence of myxedema if careful and frequent observations were not made. The use of larger doses in a routine manner would also have to await extensive clinical studies on the safety of larger amounts of this compound.

Confirmation of the impression that doses up to 150 mg. daily are not grossly excessive is provided by observations on maintenance doses and by the quantities which have been found to eventuate in hypothyroidism. Few patients were carried on the maximal dose of 150 mg. long enough to tell whether it would always lead to hypothyroidism. Three patients showed clear clinical evidence of hypothyroidism or an excessively elevated serum cholesterol after receiving 150 mg. daily for two and one-half, four or five

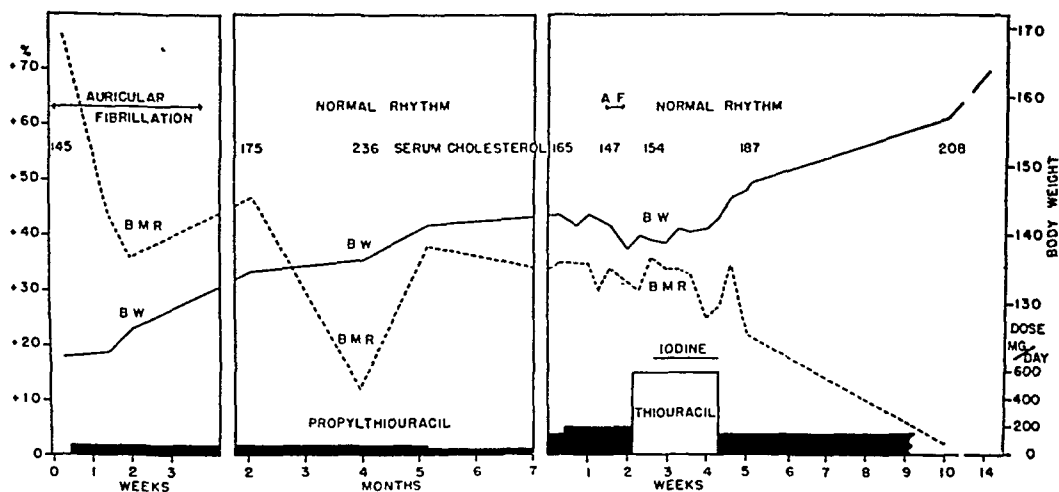


FIG. 2. Effects of various doses of propylthiouracil on the body weight, basal metabolic rate and serum cholesterol of a case of severe Graves' disease associated with advanced thyrotoxic myopathy and thyrotoxic heart disease with auricular fibrillation. This 53 year old man had been treated for two years as a case of lead poisoning because of the muscle paresis. Partial improvement had attended the use of potassium iodide. The initial metabolic response to 75 mg. daily of propylthiouracil was prompt and normal cardiac rhythm was restored in 18 days. When the dose was reduced to 50 mg. a relapse occurred which was only slowly brought under control with 150 mg. daily. Thiouracil in a dose of 0.6 gm. daily with full doses of Lugol's solution did not seem to be more effective than the propylthiouracil.

months respectively. Two developed hypothyroidism from 100 mg. daily, one from 50 mg. and one while taking 25 mg. This last case exhibited a marked rise in the serum cholesterol in addition to clinical evidence of early myxedema eight months after treatment started and four months after the dose had been reduced to 25 mg. daily. Whether this represents an unusually striking response to the drug or whether it was a spontaneous hypothyroidism cannot be determined.

This study of dosage leads to the conclusion that 150 mg. daily is an appropriate initial dose for severe and moderately severe cases of hyperthyroidism and that, although many cases would respond to less, smaller doses such as 75 or 100 mg. daily might best be used only in milder forms of the disease. The initial dose should be continued until all manifestations

of the disorder have disappeared, and only then should it be reduced to 100 or to 50 mg. daily. Later on, during the maintenance period, the quantity given daily can further be reduced to 50 or 25 mg.

Two of the most difficult cases encountered in this series are summarized in figures 2 and 3. The responses of these two patients illustrate several points of importance. In each instance a small initial dose brought about a

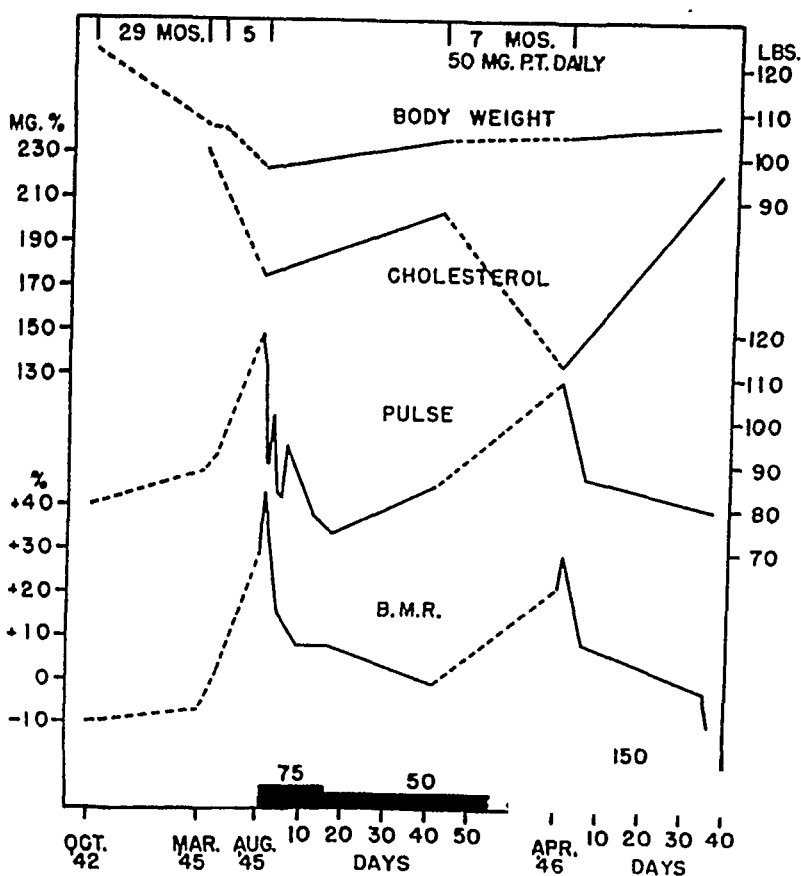


FIG. 3. The course of a patient treated with propylthiouracil illustrating the difficulty in determining the minimal effective dose. This 53 year old woman was treated in the hospital for a fractured wrist in 1942 before any evidence of hyperthyroidism was evident. She entered the hospital again in March 1945, because of recurrent bouts of diarrhea, weight loss, easy fatigue, nervousness and sweating. The diagnosis was not made until a subsequent admission five months later. Propylthiouracil in a dose of 75 mg. daily brought about prompt and striking improvement. During a seven month residence in Florida 50 mg. daily failed to maintain the remission, and 150 mg. daily were used to evoke a second response which, though more complete, was no more rapid than that induced by 100 mg. daily. A maintenance dose of 100 mg. daily subsequently seemed to be required.

prompt though incomplete response. In both cases the dose was reduced before complete health had been restored, and when hyperthyroidism had returned, prolonged treatment with a large dose was required to restore normal health. In retrospect it is apparent that a larger initial dose continued for a longer time would have given a more satisfactory result.

The well recognized influence of previous iodine therapy in delaying the

clinical response to an antithyroid drug was observed in a number of instances in this series. A minority of patients recently under the influence of iodine exhibit a prompt response to antithyroid therapy, and consequently the greater variation in the rate of response of iodine-treated patients makes them less suitable for evaluating the effectiveness of a new drug. The extremes noted in this series were as follows. The most rapid response was seen in a woman of 28 who had received iodine for four months; prompt improvement occurred when iodine was started but control was only partial; when a skin eruption developed the iodine was discontinued, and four days later propylthiouracil was given in a dose of 150 mg. daily; within two weeks all residual manifestations of hyperthyroidism had disappeared. The longest iodine-induced delay occurred in a woman of 52 who despite full doses of iodine for four years had remained severely thyrotoxic; the iodine was discontinued when propylthiouracil was started; a dose of 150 mg. daily was continued for three months before a distinct improvement was apparent, but subsequently recovery was rapid.

SIDE EFFECTS

In this series of cases no significant side effects were encountered. As in any group of patients under observation for prolonged periods of time, minor illnesses of one kind or another developed in some during the course of therapy. With the possible exception of itching of the skin with or without a mild urticarial rash, these intercurrent episodes followed no recognizable pattern, but some of them may have been caused by the drug.

Transient itching of the skin was noted by four patients, and in two of these a frank urticarial eruption was seen. In only one instance was the drug stopped, but in this case treatment was resumed 48 hours later and continued for three months without a recurrence of symptoms. In the others the itching subsided within a few days without withdrawing the medication. It is significant that itching of the skin was complained of by three patients before the treatment was started. Two patients complained of headache during the first few days of therapy. They considered that the headache was unusual for them and felt that the medication was responsible. In one the drug was omitted for 36 hours, but the headache continued until two days after it was resumed. Thereafter the headache did not return. The second patient continued the medication and the headache cleared in four days. One man developed what appeared to be an acute upper respiratory infection during the second month of treatment. There was a severe sore throat and a temperature of 100.5° F., but the leukocyte count remained normal; other members of the family had a similar disorder. Medication was not interrupted and recovery was complete in five days. A month later he complained of migratory joint pains involving one hip, the knees and the ankles. As he had suffered from subdeltoid bursitis prior to treatment, the arthralgia was not considered to be caused by the drug. Therapy was continued, and when

the hyperthyroidism was completely controlled the joints improved and he remained symptom-free during the ensuing four months of treatment.

One patient died while being given propylthiouracil. This man of 52 with advanced cirrhosis of the liver was thought to have hyperthyroidism as well, and propylthiouracil in a dose of 75 mg. daily was administered. The clinical course was that of progressive hepatic failure; the introduction of propylthiouracil therapy did not seem to modify the condition one way or the other, and he died in hepatic coma three months after treatment was started.

In retrospect it would appear likely that most of these episodes were unrelated to propylthiouracil therapy, but it is possible that the two episodes of urticarial eruption were manifestations of drug sensitivity. The significant finding was that no serious reactions occurred and that in no instance was it necessary to abandon this form of treatment.

Particularly instructive were the patients who had previously exhibited intolerance to thiouracil and to thiobarbital. Five patients were given propylthiouracil after they had experienced severe febrile reactions to thiouracil. In two of these the fever had been accompanied by significant neutropenia. One of these patients and one other had had febrile reactions accompanied by an extensive skin rash following the use of thiobarbital. In none of these six patients were any untoward effects observed following the use of propylthiouracil.

It is also of interest that three of the patients in this series of 100 were referred for treatment because of intolerance to iodine. Each of these was treated with propylthiouracil without mishap.

Doubtless some sensitivity reactions will be encountered if this compound is extensively employed. There are few drugs which when continually administered do not provoke untoward reactions in a certain percentage of individuals. However, in the therapy of a serious disease the absence of significant side effects in 100 consecutive cases indicates that the risk attending the use of this drug is not a material consideration.

SUMMARY

One hundred unselected cases of hyperthyroidism encountered during the course of one year were treated with propylthiouracil. Considerable individual variation in the minimal effective dose was observed, some patients requiring as little as 50 and some others as much as 150 mg. daily to restore metabolic equilibrium. It was concluded that 50 mg. every eight hours is approximately the optimal dose for the routine treatment of the more severe cases, that 50 mg. twice daily is adequate for milder ones, and that an effective dose should be continued until all manifestations of the disease have been controlled before smaller maintenance doses are substituted.

The use of this medication was unattended by significant side effects, and it is therefore suggested that it is a safe and satisfactory compound for the treatment of hyperthyroidism.

ACKNOWLEDGMENT

We are indebted to the many physicians who have permitted us to include their private patients in this study and to the staffs of the Pratt Hospital and Boston Dispensary for their generous assistance.

BIBLIOGRAPHY

1. VAN WINKLE, W., HARDY, S. M., HAZEL, G. R., HINES, D. C., NEWCOMER, H. S., SHARP, E. A., and SISK, W. N.: The clinical toxicity of thiouracil, a survey of 5,745 cases, Jr. Am. Med. Assoc., 1946, cxxx, 343.
2. ASTWOOD, E. B., and VANDERLAAN, W. P.: Thiouracil derivatives of greater activity for the treatment of hyperthyroidism, Jr. Clin. Endocrinol., 1945, v, 424.

OBSERVATIONS ON THE USE OF THIOURACIL *

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IN the two and one half years that have elapsed since Astwood's¹ discovery and use of the potent agent, thiouracil, numerous investigators have fully confirmed his original observations and have added much useful data regarding the behavior of this chemical substance. This invested effort is now beginning to show returns in increased interest in and better understanding of the general nature of its action on the thyroid, and in a growing recognition of the value of thiouracil for combating the thyrotoxic state and reducing it to a safe tractable level.

A number of facts regarding thiouracil appear to be generally accepted. The best explanation of the action of thiouracil is that it interposes a block at the acinar cell of the thyroid stopping production of thyroxin. This action unbalances the normal reciprocal relationship between the thyroid and the anterior pituitary whereby the production of thyroxin and of thyrotropic hormone are each determined by the quantity of the other of these hormones in the circulation. As the amount of thyroxin diminishes, increasing quantities of thyrotropic hormone are elaborated which stimulate hyperplasia of the acinar cell but without increasing the production of thyroxin. A measurable change in the body metabolism occurs only after all of the pre-formed thyroxin has been used up, thereby explaining the delay in appearance of drug action.

Thiouracil-induced hyperplasia differs from that induced by the cyanides in that it is not at all influenced by iodine, although it may be retarded by previously administered iodine stored as thyroxin, which tends to inhibit the pituitary. Thiouracil-treated rats fed radioactive iodine show very little formation of diiodotyrosine and thyroxin, but when thiouracil is withdrawn, the amount of radioactive iodine converted to thyroxin increases, the full concentrating capacity of the thyroid being restored in about 14 days after withdrawal of the thiouracil.

Thiouracil is rapidly absorbed from the intestinal tract, reaching a peak blood level in 15 to 30 minutes after 0.1 to 0.2 gm. has been administered to a normal fasting man. From this point there is a gradual decline in the blood level with complete disappearance in 48 to 72 hours. The blood concentration may be maintained fairly well by repeated frequent administration of small doses. The drug enters the cellular elements rapidly, the quantity in the red blood corpuscles being approximately twice that of the

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The thiouracil was supplied through the courtesy of Dr. Stanton M. Hardy, Lederle Laboratories, Inc.

leukocytes, but proportionately higher in the latter than in the former. Bone marrow attracts the largest proportion of the drug, the thyroid, ovaries and pituitary holding lesser amounts in the order mentioned. Alterations of thyroid structure affect drug storage so that more is stored in adenomatous than in normal tissue. A large part of ingested thiouracil is rapidly destroyed in the intestinal tract so that none is found in the stools. The remainder is excreted mainly in the urine.

Very few tissue changes other than the characteristic hyperplasia in the thyroid gland have been observed. The McKenzies³ noted basophilia ("thyroidectomy cells") in the anterior pituitary of thiouracil-treated animals, and a similar finding was reported recently by the author⁴ in the case of a woman who died suddenly of cerebellar hemorrhage while she was under treatment with thiouracil for toxic thyroidadenoma.

Benigni and malignant tumors of the thyroid have been produced in rats by the combined administration of allylthiourea and a carcinogen, 2-acetyl aminofluorene, but neither of these substances was capable of inducing thyroid neoplasia alone. It is significant that up to the present there have been no reports of malignant changes occurring either in animals or man as a result of the administration of thiouracil or thiourea.

CLINICAL EXPERIENCE

Although 91 patients have been treated with thiouracil during the past two and one half years, only 70 have been observed for a sufficient period to permit drawing definite conclusions from the experience. Of the remaining 21, only five had thyrotoxicosis, but these had been treated for too short a time. The rest consisted of three cases of questionable hyperthyroidism, three of hyperthyroidism induced by overfeeding with thyroid substance, three instances of thyroiditis, and seven patients with angina pectoris (not included in this report).

The 70 patients with thyrotoxicosis ranged in age from 16 to 82. Forty of these had toxic adenoma, the group consisting of 10 males and 30 females. There were 30 patients with toxic diffuse goiter, five of these being males and 25 females. The average initial basal metabolic rate was plus 26 per cent for those with toxic adenomata and plus 30 per cent for the toxic diffuse goiters. In this latter group 16 patients had had previous thyroidectomies, 11 having had one, 3 two, and 2 three.

DOSAGE OF DRUG

Early in this study patients were given 0.8 gm. of the drug daily, divided into four equal doses of 0.2 gm. This was in keeping with the generally recommended dosage of 0.8 gm. to 1.2 gm. per day. As it became recognized that large doses offered no special advantage, the daily amount was reduced to 0.6 gm. per day, and now the average daily initial dose is between 0.4 and 0.6 gm. It is best that the interval between doses not be prolonged

beyond 12 hours. Response to the drug was satisfactory in all except one, a patient with diabetes mellitus and toxic adenoma who had been under treatment with iodine for six years before starting thiouracil. After 17 months' administration of thiouracil without response, it was replaced by 0.6 gm. thiourea daily for the next three months, but without notable effect. It is quite likely that this failure may have been due to the long continued previous administration of iodine which interfered with the absorption of the thioureas. The experience of other investigators indicates a failure in about 2 per cent of treated cases, with the cause not always evident.

Most patients reported subjective improvement within one to two weeks after beginning treatment, but objective signs of response appeared after a somewhat longer interval. Of the patients who had had iodine, those with toxic diffuse goiter required an average of 8.2 weeks before responding satisfactorily, while those with toxic adenoma required but 6.6 weeks. Where there was no previous treatment, the former (toxic diffuse) took 6.6 weeks whereas the latter took six weeks. The patients who had had previous operation required an average of 6.2 weeks before remission appeared. These figures vary somewhat from the reported experience which credits toxic diffuse goiter patients and those previously untreated with iodine with an earlier response. Generally, however, six to seven weeks may be considered as the shortest period in which to expect a remission.

As improvement appeared, dosage was reduced. The initial 0.6 gm. daily dose was reduced to 0.4 gm. after three to five weeks; and as remission gradually became manifest, a maintenance dose was given that would keep the patient in continuous remission without causing myxedema. In the group under observation 22 are now on a maintenance dose of 0.1 gm., 19 on 0.2 gm., 17 on 0.3 gm., 9 on 0.4 gm. and 3 on 0.6 gm. daily.

Twenty-five patients have been treated from two to six months, 25 more from seven to 12 months, 16 patients from 12 to 24 months and four from 25 to 28 months. Repeated attempts have been made to determine whether the drug may be discontinued and when it is advisable to do so. In every instance in which this was attempted before six months' treatment had been carried out, relapse occurred after an interval of three days to eight weeks. Ten patients, six with toxic adenoma and four with toxic diffuse goiter, have remained in remission for periods ranging from six to 24 months. It is significant that the period of treatment in these patients was not less than six months, the average being 13 months. Although some investigators claim sustained remission in a large number of treated patients, the average of those who continue in remission after the drug has been stopped is approximately 10 per cent. Nevertheless, it is worthwhile to discontinue the drug after from 18 to 26 weeks. If relapse occurs, its readministration brings patients back into line quite promptly.

A basal metabolic rate between plus 5 and minus 10 per cent was desirable, but was not easily maintained, particularly in those with toxic diffuse goiter. Mild grades of myxedema developed in four with toxic diffuse

goiters and two with toxic adenomata. The basal metabolic rate dropped to minus 14, 17, 27 and 32 in the former and minus 23 and 24 in the latter. Prompt recovery followed cessation of the drug for one week followed by resumption at a lower dosage level. These patients are now being given small doses of thyroid substance, ranging from $\frac{1}{4}$ to $\frac{1}{2}$ grain daily, in addition to the thiouracil. This appears to be a logical supplementary treatment in patients who are being given thiouracil for extended periods of time. Here it is conceivable that an increasing need for thyroxin may develop because of the possible total suppression of its production. Accordingly, the exhibition of small amounts of thyroid substance after the overactive thyroid gland has been depressed by thiouracil appears logical where prolonged medical treatment is planned. Early concomitant administration with thiouracil is not advisable, but rather it is preferable to begin after remission has become fully manifest. Twelve patients in this series are now on combined therapy; seven have toxic diffuse goiters, while five have toxic adenomata.

CHANGES IN THE THYROID GLAND

Some increase in size of the thyroid was noted in the early weeks of treatment and was usually associated with softening of the gland. These changes were more pronounced in the toxic diffuse goiters, but in either type they rarely reached alarming proportions. This enlargement caused tracheal compression in three patients with large adenomata and in one instance hemorrhage into the gland was found at operation. Gradually, however, the gland tended to recede and become smaller and in many instances has diminished in size remarkably though it has never become totally impalpable.

EXOPHTHALMOS

Slight increase in exophthalmos was observed in only one patient during treatment, and this has remained stationary after subtotal thyroidectomy. Of nine patients with post-operative residual hyperthyroidism and exophthalmos, three showed no change in the exophthalmos while six showed measurable improvement.

THYROTOXIC AURICULAR FIBRILLATION

Four patients with thyrotoxic auricular fibrillation, all taking digitalis, showed a return to normal sinus rhythm as soon as the thyrotoxic state was controlled by thiouracil. None of these patients have had further need for digitalis. Obviously, where the fibrillation is secondary to disturbances other than thyrotoxicosis, satisfactory control is not to be expected.

REACTIONS

Unfavorable reactions to thiouracil have been quite thoroughly publicized, and rightfully so, since this is a new drug, potent in action, with

harmful potentialities in some of its side effects. Indiscriminate condemnation is not indicated by these warnings. Rather are they to be taken as cautionary guides in the proper use of this potent but valuable drug.

Agranulocytosis has been the outstanding unfavorable reaction, with drug fever ranking next as a serious disturber. The former complication is likely to occur without warning and without previous leukopenia or granulocytopenia. The unpredictability of its appearance, together with the established belief that fatalities run close to 100 per cent, has caused many to shun even mention of thiouracil. However, the danger has been exaggerated. Although this is an alarming complication, its incidence is no higher than 2.5 per cent and its mortality 10 to 12 per cent. In fact, the mortality from agranulocytosis in all thiouracil treated cases is 0.4 per cent, and its further reduction is fully expected now that it has been found that cessation of administration of the drug and continuous parenteral administration of penicillin will allow the patient's bone marrow to recover from its suppression without the intervention of fatal infection. One patient in this series developed agranulocytosis on the fifty-ninth day after she had had 10.1 gm. of thiouracil. Recovery followed after one week of continuous penicillin therapy.

Unfortunately there is no known method of prevention. Large doses of vitamin concentrates, pyridoxine, folic acid and liver extract have all been tried without avail. We tried testing 100 people intradermally with serum obtained from a patient under treatment with thiouracil (with a serum level of 3 to 4 mg. per cent) but dropped the investigation when no reactions were noted, particularly in one patient who had had two separate episodes of drug fever from oral thiouracil.

At present the only safe procedure to follow is to observe patients at regular intervals, making blood counts at first every week and later every two to four weeks, and making certain that these patients do not travel away from home, placing themselves out of reach.

One significant observation is the seeming preponderance of patients with toxic diffuse goiter among those developing agranulocytosis. Correspondence with 10 of the leading investigators in the field and a survey of the reported cases of this complication substantiate this finding. The obvious inference is that patients with toxic diffuse goiter, being more prone to this disturbance, must be watched more closely while under treatment.

Five patients in this series developed drug fever with chills, malaise and sore throat but without change in the blood picture, after varying periods of drug administration. One developed the reaction during the thirty-sixth week and one each after 14, 8, 7, and 3 days. A subsequent trial with a small dose of the drug produced the same reaction, so that its use was abandoned in all of these patients. Two patients developed a generalized urticarial eruption which cleared within a few days after the drug was discontinued.

INDUCED HYPERTHYROIDISM

Hyperthyroidism induced by overtreatment with thyroid substance appears to respond quite promptly to thiouracil therapy. Three instances have been observed.

CASE REPORTS

The first, a man aged 47, with a reported basal metabolic rate of minus 30 per cent, had been taking 6 gr. thyroid substance because of sexual impotence for a period of six weeks. He had lost 10 pounds, was nervous and irritable, with palpitation and tremor, and the basal metabolic rate was plus 22 per cent. The thyroid gland was not palpable. Disappearance of all symptoms with gain in weight and return of the basal metabolic rate to a normal level occurred after eight weeks of thiouracil (0.4 gm. daily).

The second patient, a man aged 38, had been taking 3 gr. thyroid substance daily for six months because of tiredness, backache and a low basal metabolic rate. He lost weight, had tachycardia, and in spite of replacement of thyroid substance by Lugol's solution, developed auricular fibrillation. This continued uncontrolled for four months until he was started on thiouracil. After two weeks, normal sinus rhythm had been reestablished and the basal metabolic rate had dropped from plus 39 per cent to plus 21 per cent. A slight enlargement of the thyroid was found. He remained under control during the next nine months while taking 0.2 gm. thiouracil daily, but when this was discontinued, his symptoms recurred at the end of four weeks and he is still obliged to take 0.1 gm. daily to remain in remission.

The third patient, a woman aged 35, was for some fantastic reason placed on 32 gr. thyroid substance daily following a double mastectomy for cystic mastitis. She became extremely nervous and irritable, was constantly hungry and had marked urinary frequency. This unusual treatment was followed for six months. Then the dosage was reduced and kept at from 21 to 28 gr. thyroid substance daily for the next 3½ years. At this point the patient decided she was not improving and stopped the medication.

When first seen she had had no medication for two weeks. She was extremely nervous and restless, had a fine tremor of the hands, but showed no thyroid enlargement, eye signs or tachycardia. The basal metabolic rate was plus 13 per cent. After four weeks on 0.4 gm. thiouracil daily she gained five pounds, the basal metabolic rate was plus 5 per cent and the original symptoms were much less pronounced. Gradually the drowsiness, urinary frequency, and, finally, the extreme hunger, disappeared after three months' treatment.

DIABETES MELLITUS AND HYPERTHYROIDISM

In the past this serious combination has been controlled with varying success either by thyroidectomy, when the patient could be stabilized sufficiently to withstand operation, or by use of iodine. The positive action of thiouracil in thyrotoxicosis early suggested its use in this combined disturbance, but reports on its use are variable insofar as the expected improvement in the diabetes is concerned.

Eight patients with this condition have been treated with thiouracil. These ranged in age from 27 to 66; five were females, and three males. In one patient both the thyrotoxicosis and diabetes had been successfully controlled by iodine. In this case there was no response to thiouracil. Four

of the remaining seven patients also showed a marked improvement in their diabetes as evidenced by levelling of blood sugar fluctuations, absence of glycosuria, and reduction in dosage or total elimination of insulin. The remaining three, although developing satisfactory remission in the thyrotoxicosis, failed to show improvement in the diabetes. The reason for this difference in reaction became apparent when it was noted that all patients in the first group had toxic adenoma or secondary hyperthyroidism, the diabetes having preceded the thyrotoxicosis. The patients in the second group all had toxic diffuse goiters (two with previous thyroidectomy) or primary hyperthyroidism, which had appeared before the diabetes.

When the case reports in the literature were restudied and classified⁵ there were 13 treated patients of whom four had improved whereas nine had not. The patients improved were all instances of toxic adenoma whereas the others had toxic diffuse goiter.

PRE- AND POST-OPERATIVE USE OF THIOURACIL

Eleven patients in this series were subjected to thyroidectomy after previous preparation with thiouracil. Five of these had toxic diffuse goiter and six toxic adenoma. Before the combined use of thiouracil and iodine was recommended by Bartels and Lahey, patients were prepared with thiouracil alone. The surgeons encountered varying degrees of increased vascularity and friability in all instances, least notable in those brought to a full state of remission before operation.

Two patients prepared with thiouracil and iodine developed myxedema on the second and third post-operative day. In all probability the level of thyroxin production was quite low at operation, and the myxedematous state may well have been precipitated by the resection of the gland and the temporary functional depression of the residual tissue. Improvement in these patients followed promptly on the administration of small amounts of thyroid substance. Two patients with fulminant toxic diffuse goiters uninfluenced by iodine responded only slowly to thiouracil. In each instance, the addition of iodine after four months of thiouracil produced a summation of effect and permitted preparation for and performance of thyroidectomy. Surgeons are generally agreed that patients prepared with thiouracil constitute as slight a risk as those with non-toxic adenoma and their post-operative course is as smooth and uneventful.

Sixteen patients in this series had had thyroidectomy previous to treatment with thiouracil, three having had two and two having had three operations. All of these patients originally had true Graves' disease. Response to thiouracil was both prompt and satisfactory in all of these patients although many had been taking iodine without improvement for varying periods of time. In four, a second thyroidectomy was under consideration but was deferred because of the improvement. In none of these patients, however, has it been possible to discontinue the drug without a return of symptoms, although

some of them have been under treatment for nearly two years. It is apparent that here the original causative factor is uninfluenced by the thiouracil which controls only the effect.

ACUTE THYROIDITIS

In the past, patients presenting this rare complication remained ill for a protracted period with marked tenderness and swelling over the thyroid, difficulty in swallowing, fever, palpitation and elevated basal metabolism. Treatment consisted mainly of local application of ice, administration of Lugol's solution and roentgen therapy. Relief was slow and protracted, often taking several months. In some instances suppuration necessitated surgical drainage. The advent of thiouracil has changed this picture appreciably. King and Rosellini² were the first to call attention to the promptness with which acute thyroiditis subsides when thiouracil is administered, eight of their eleven patients having been promptly cured.

Three patients in this series had acute thyroiditis which subsided promptly following thiouracil administration. All had been treated symptomatically with iodine and local application of ice for varying periods of time. The condition subsided in 8, 10, and 14 days respectively, and the thyroid enlargement in the first two patients disappeared completely at the end of three months. Thyroidectomy was performed on the third patient at the end of two months for an adenoma that had been present for 20 years.

DISEASE TESTED WITH THE DRUG

As with any potent therapeutic drug, there arise instances in which the procedure may be reversed, and instead of testing the drug against the disease, the latter, particularly if it is borderline or questionable, is tested with the drug. Clinically, a variety of disturbances with certain characteristics simulating hyperthyroidism present themselves for accurate diagnosis. These occur mainly in patients with anxiety neuroses or in those with neurocirculatory asthenia. The occult forms of hyperthyroidism responsible for auricular fibrillation or accentuating diabetes mellitus also belong in this group.

In the past iodine has been used in these patients with varying success, and it was thought that a more potent depressive agent such as thiouracil might prove more useful and decisive. Accordingly, the drug was used in several patients in whom a diagnosis of hyperthyroidism was thought likely but in whom many of the distinctive features were lacking.

The first of these was a 39 year old white male complaining of insomnia, nervousness, palpitation, tremor of the hands and a weight loss of six pounds during a period of six months. He presented no thyroid enlargement or eye signs, but the palms were warm and moist, there was tachycardia, and the basal metabolic rate was plus 7 per cent. Because of a history of domestic and financial difficulties and because of heavy use of tobacco, it was felt that this was an anxiety state coupled with symptoms of chronic tabagism. However, to rule out the presence of a thyrotoxic com-

ponent a daily dose of 0.4 gm. thiouracil was administered during a period of nine weeks. The basal metabolic rate readings at two week intervals were plus 4, plus 6, zero and plus 2 and no improvement was noted in the patient's condition.

A second patient, a 42 year old white unmarried woman, had been under observation for a year because of exhaustion, nervousness, insomnia, palpitation and cold clammy hands and feet. She was 66½ inches tall and weighed 111 pounds. There was scoliosis of the thoracic spine, and the lower pole of the right kidney was movable and palpable. The blood pressure was 100 mm. Hg systolic, 60 mm. diastolic. After the usual therapy for neurocirculatory asthenia had produced little improvement, a trial of thiouracil was instituted. The thyroid was not palpable, and there were no eye signs present. The basal metabolic rate was minus 3 per cent. She tolerated 0.6 gm. of thiouracil daily for a period of three months with no improvement in her general condition. The final basal metabolic rate reading was minus 17 per cent.

The third patient, seen only recently, was a white woman aged 56, with diabetes mellitus that was extremely difficult to control (she required as much as 200 units insulin per day) who was found to have a small palpable nodule in the right lobe of the thyroid and a basal metabolic rate of plus 10 per cent. There were no other signs of hyperthyroidism, but it was believed worthwhile to use thiouracil to determine whether this was present. The response was quite dramatic. Within two weeks, on 0.4 gm. per day, the basal metabolic rate had dropped to plus 5 per cent, the thyroid nodule was larger and softer, and the blood sugar had fallen to 150 mg. per cent on only 40 units insulin daily.

Evidently thiouracil can serve usefully in the differentiation of borderline disturbances, but its administration in such conditions must be carefully watched and limited to as short a period as is essential for arriving at a definite diagnosis.

SUMMARY AND CONCLUSIONS

From the observations reported here and those of other workers in the field, the following conclusions regarding thiouracil appear valid and firmly founded:

1. The drug is a potent thyroid-depressing agent which blocks the acinar cells of the thyroid, preventing the formation of thyroxin and indirectly liberating excess thyrotropic hormone from the anterior pituitary, causing marked thyroid hyperplasia. When its action is fully established there occurs a basophilia in the anterior pituitary similar to that which follows thyroidectomy.

2. It is effective in both toxic adenoma and toxic diffuse goiter asserting its full action after an average of six weeks of administration. Previous administration of iodine appears to retard the action somewhat. Failures occur in about 2 per cent of treated patients.

3. Permanent remission occurs only in about 10 per cent of patients after stopping the drug. The remainder tend to relapse after a varying period of time. The relapse rate is highest in those patients who have been treated for less than 18 to 26 weeks. At present it is still not possible to predict how long a period of treatment is necessary for inducing permanent remission.

4. Myxedema may readily follow the use of thiouracil, but this may be promptly alleviated by stopping the drug for a short time and administering small quantities of thyroid substance. In fact it would appear logical, during the prolonged use of thiouracil, to administer thyroid substance also, thus supplying the body with its minimal need for this agent.

5. Some increase in size of the thyroid, as well as softening, occurs in many instances. Rarely there is a rapid increase in size with resultant pressure symptoms. Ultimately the gland tends to recede and become smaller.

6. Exophthalmos is rarely increased. In fact, six of nine patients with this condition present before treatment showed improvement.

7. Thyrocardiacs with auricular fibrillation show a return to normal sinus rhythm if the disturbance is caused only by thyrotoxicosis.

8. Toxic reactions occur in about 13 per cent of treated cases. Agranulocytosis, the most serious reaction, has an incidence of 2.5 per cent and a mortality rate of 10 to 12 per cent which probably will be reduced by treatment with penicillin administered parenterally. It appears most likely to occur in patients with toxic diffuse goiter, so that this group of patients requires close watching. Drug fever is next in incidence and appears to be an expression of drug idiosyncrasy. Patients showing this reaction are usually unable to take the drug.

9. It is especially useful in hyperthyroidism induced by overdosage with thyroid substance; in diabetes mellitus complicated by hyperthyroidism; in acute thyroiditis; and as a diagnostic aid in borderline hyperthyroidism.

10. It is today the most effective agent for inducing remission in thyrotoxicosis and has proved itself extremely useful in the preparation of patients for thyroidectomy, making for simpler, less costly pre-operative preparation and smoother shorter convalescence.

Evaluation of its use medically can not be made as readily at the present time because of the tendency to relapse after cessation of treatment and the limited knowledge regarding toxicity. However, it has a dominant place in the treatment of the aged patient with toxic adenoma who is a poor operative risk, and in those with recurrent thyrotoxicosis. Only time will tell whether it will ultimately become the treatment of choice in toxic diffuse goiter.

BIBLIOGRAPHY

1. ASTWOOD, E. B.: Treatment of hyperthyroidism with thiourea and thiouracil, Jr. Am. Med. Assoc., 1943, cxxii, 78.
2. KING, B. T., and ROSELLINI, L. J.: Treatment of acute thyroiditis with thiouracil, Jr. Am. Med. Assoc., 1945, cxxix, 267.
3. MACKENZIE, C. G., and MACKENZIE, JULIA B.: Sulfonamides, thioureas and thyroid, Endocrinology, 1943, xxxii, 185.
4. REVENO, W. S.: Effect of thiouracil on human tissues, Jr. Clin. Endocrinol., 1945, v, 403.
5. REVENO, W. S.: Thiouracil effect in diabetes mellitus complicated by hyperthyroidism, Am. Jr. Med. Sci., 1946, ccxi, 174.

THE DIAMIDINES IN CHEMOTHERAPY: A SURVEY OF RECENT DEVELOPMENTS WITH A NOTE REGARDING THERAPEUTIC TRIALS IN PATIENTS WITH RHEUMATOID ARTHRITIS *

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RECENT advances in the field of therapy for protozoal diseases, though not so spectacular as the discoveries of sulfonamides and penicillin, have nevertheless been significant and deserving of wider attention than they have yet received in this country.

The most interesting and most promising of these discoveries concerns the parasitidal effects of the family of strongly basic organic preparations known as diamidines. These compounds have been shown to possess value in treatment of leishmaniasis and trypanosomiasis, diseases which affect many inhabitants of great portions of the earth and cause endless suffering. Compounds of this group also possess bactericidal properties, and for this reason there is hope that further important uses may be found for these drugs.

HISTORICAL

Behind the development of these compounds lies an interesting story of a scientific search which followed a tenuous thread of information for nearly 30 years and finally led to a discovery which may prove to be momentous.

The story of this search was told by Professor Warrington Yorke³⁵ in an address delivered at a meeting of the Royal Society of Tropical Medicine and Hygiene in 1940. His story illustrates a strange and provocative paradox: in the field of scientific research even a misconception may, at times, lead to important discoveries.

As early as 1911, trypanosomes were observed to survive longer in citrated blood if glucose was added to the medium, and later it was shown that trypanosomes require relatively large amounts of glucose for maintenance and growth. Cultured in citrated blood these organisms gradually became motionless and died, but inanimate, apparently moribund organisms, could be reanimated by the addition of blood serum or glucose-containing solutions to the medium. A study of this phenomenon showed that glucose was the substance responsible for reanimation of the inanimate organisms.

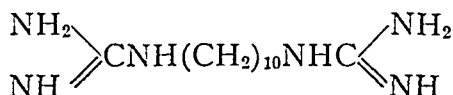
It was also found that in the terminal phases of experimental trypano-

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somiasis animals often showed hypoglycemia, a fact which pointed further to a relationship between these infections and the availability of glucose to the infecting parasite.

These observations led to a search for a therapeutic agent against trypanosomiasis among hypoglycemia-producing chemicals. Insulin was studied first but was shown to be ineffective. The search then turned to synthalin. As may be seen in the diagram, synthalin consists of an alkyl chain buttressed at either end by a guanidine radical, a carbon atom having all four of its valences attached to hydrogen-carrying nitrogen atoms.



SYNTHALIN

This compound was found to be a potent protozoicidal agent against trypanosomal infections in rats and as little as one part in 200 million killed trypanosomes in cultures. However, the protozoicidal effects of synthalin appeared to have no relation whatsoever to the lowering of blood sugar.

The high degree of toxicity of synthalin in relation to its therapeutic effectiveness stimulated an examination of other compounds of this general type in a search for a potent and less toxic drug. A large number of new compounds were synthesized including alkyl- and alkylene-amines, amides, isethioureas and guanidines. The most effective of these were found to be certain alkyl and aromatic preparations having terminal amidino groups similar to those of the synthalin molecule. Subsequent work has shown that these ammoniacal polar groups are responsible for the therapeutic effects of the series. The central alkyl and aromatic groups serve as carriers for the active amidino terminal radicals, and give the compounds varying physical properties and varying degrees of toxicity.

Especially satisfactory results were obtained in the laboratory treatment of experimental protozoal infections with three compounds: (1) 4:4'-diamidino stilbene, now known as "stilbamidine," (2) 4:4' diamidinodiphenoxy pentane now known as "pentamidine," and (3) 4:4' diamidinodiphenoxy propane now known as "propamidine." These compounds appeared to possess a species rather than a class specificity against trypanosomes as *T. rhodesiense* and *T. congolense* infections were shown to be helped whereas *T. cruzi* infections were not.²² Further studies showed that animals infected with babesiasis or leishmaniasis could be cured, but certain spirochetal infections were not affected.

Thus, an attempt to find a cure for trypanosomal infections among blood sugar lowering compounds had resulted in the discovery of effective chemotherapeutic compounds whose protozoicidal powers did not seem to be related to the ability to lower blood sugar. What is more, these compounds were also found to have therapeutic value in leishmaniasis of animals⁴ so that

therapeutic trials in man were clearly justified: These are now in progress, and the results published thus far are summarized below.

PHARMACOLOGY OF DIAMIDINES

Toxicity in Laboratory Animals. A study of the toxic properties of diamidines showed that these drugs were well tolerated by mice even when they were administered in relatively large amounts,³⁵ whereas therapeutic activity was present even with extraordinarily small doses. These animals tolerated doses up to one milligram to 20 grams of body weight, whereas as little as 0.005 to 0.00625 milligram to 20 grams of body weight would suffice to clear the peripheral blood of Babesial parasites in more than 50 per cent of infected animals tested. Doses of 2 mg. per 20 gram mouse were almost invariably fatal, the animals showing narcosis, dyspnea, tremors and convulsions within a few minutes after the injection. Death generally ensued in about one hour. Fractional doses of 0.1 mg. per 20 gram animal could be given daily for long periods without producing signs of intoxication.

In rabbits, the maximum tolerated dose of stilbamidine or pentamidine given by the intravenous route was 20 mg. per kg. In cats and dogs, doses of 5 to 10 mg. per kilogram were generally followed by a marked fall in blood pressure, but the animals recovered within a few minutes.

Devine¹⁰ found that successive small doses of diamidines were generally well tolerated, but nitrogen retention was evident after doses of 15 mg. per kilogram in rabbits. Higher doses produced hyperglycemia of short duration as well as nitrogen retention. No significant evidence of hepatic damage could be demonstrated other than the hyperglycemia which was considered to be a possible sign of hepatic toxicity.

In cattle, Daubney and Hudson⁸ found that doses of pentamidine large enough to cause death produced edema of the gastric mucosa, fatty degeneration of the liver, petechiae in the endocardium and epicardium and congestion of the meningeal vessels. These authors noted that cattle tolerate stilbamidine in doses at least four times higher than the fatal dose of pentamidine.

Toxicity in Man. The earliest trials of diamidines in man showed that administration of doses exceeding 1.0 mg. per kilogram of body weight would provoke flushing of the face, epigastric discomfort, headache, a rapid pulse, sweating, retching and occasionally vomiting in some patients. However, these symptoms passed within half an hour and often failed to reappear after the second or third injection.

Napier and Sen Gupta²⁸ and Sen Gupta³¹ reported that among 100 patients with leishmaniasis treated with 4:4' diamidino-diphenyl-ethylene, four a few months after injection had developed numbness and partial anesthesia of the forehead but no evidence of any other neurologic disturbance. They concluded that these symptoms had been caused by a toxic degenerative lesion of the pons, and noted also that this toxic reaction tended

to improve spontaneously with the passage of time. Later Sen Gupta⁸¹ reported a similar reaction in 10 additional cases following stilbamidine therapy.

Solutions of unsaturated diamidines should be freshly prepared before use or kept away from light according to Fulton and Yorke,¹⁸ who reported in 1942 that solutions of stilbamidine increase in toxicity on exposure to sunlight.

Although these drugs appear to be relatively safe, Henry and Grindley¹⁸ reported that in Sudan, treatment of leishmaniasis with both antimonials and stilbamidine resulted in some fatalities. Although they did not report details of their cases they stated that occasional fatalities had occurred either during treatment or shortly after termination of treatment when the patient was considered cured of kala-azar. Sometimes death was said to have occurred after a latent period of some weeks, suggesting a cumulative toxic reaction. No other similar reports of fatal reactions during therapy for leishmaniasis had appeared to the time of writing of this review, and the significance of these observations is uncertain as authorities on kala-azar have repeatedly reported the occurrence of sudden and unexpected deaths in patients with this disease.

The case report of a patient whose death occurred during therapy with pentamidine for trypanosomiasis has recently been published by McComas and Martin²⁴ but this observation must also be interpreted cautiously in this serious and often fatal disease.

Distribution of Diamidines in the Body. Very little information is available regarding this matter, as no method has been found for the quantitative estimation of these compounds. In 1941 Hawking and Smiles¹⁷ reported stilbamidine solutions exposed to ultra violet light fluoresced brightly even in dilutions of 1/100 to 1/1000 million. Utilizing this observation, the authors found that stilbamidine could be demonstrated in the cells of the liver, kidney, small intestine, skin, hair and vas deferens of the injected mouse. Particularly strong concentrations were noted in the granules of the trypanosomes, suggesting that the drug had a particular affinity for these parasites. They found that stilbamidine was excreted in the urine in high concentrations during the first seven hours after administration, but after two days the amount excreted was extremely small. None was excreted in the bile. The presence of blood in an organ was reported to mask this fluorescence.

By using this same technic Henry and Grindley¹⁸ showed that 10 per cent of stilbamidine injected intravenously was excreted in the urine within two and one-half days following the injection.

CLINICAL TRIALS

Diamidines in Treatment of Leishmaniasis. Both stilbamidine and pentamidine have been given to patients with leishmaniasis with favorable

results. The effectiveness of stilbamidine, however, appears to be somewhat greater than that of pentamidine. An analysis of the reported studies of the treatment of patients with this disease is recorded in table 1.

Diamidines in Treatment of Trypanosomiasis. The effectiveness of the diamidines in treatment of human trypanosomiasis cannot yet be finally assessed. The reports published thus far indicate that these drugs are notably effective for patients with the disease in its early phases but less potent in the later stages. Table 2 presents a summary of the published reports of these clinical studies.

TABLE I
Clinical Trials of Diamidines in Leishmaniasis

Author	Disease Treated	No. of Cases	Drug Used	Results
Adams and Yorke, ^{2,3} 1939, 1940	Indian Kala-azar	2	Stilbamidine	Immediate cures
Adler and Rachmilewitz, ⁵ 1939	Leishmania Infantum	1	Stilbamidine	Immediate cure
Napier and Sen Gupta, ^{27,31} 1940, 1943	Indian Kala-azar	104	Stilbamidine	98% Immediate cures
Kirk and Sati, ²⁰ 1940	Sudan Kala-azar	28	Stilbamidine	Immediate cures 23 Improved 3 Died 2
Wingfield, ³¹ 1941	Indian Kala-azar	1	Stilbamidine	Immediate cure
Adams, ¹ 1941	Indian Kala-azar	1	Pentamidine	Immediate cure
Humphreys, ¹⁹ 1942	Oral Pharyngeal Leishmaniasis	1	Pentamidine	Immediate cure
Somers, ³⁰ 1944	Sudan Kala-azar	5	Stilbamidine	Immediate cures 4 Relapse 1

Prophylactic Use of Diamidines against Trypanosomiasis. In 1944 Van Hoof, Henrard and Peel³³ reported that pentamidine is effective as a prophylactic agent against trypanosomiasis. Two volunteers injected with a single dose of 0.002 gm. or 0.003 gm. per kilogram of body weight subsequently resisted for 10 to 20 months repeated bites of infective tsetse flies. No case of sleeping sickness was found among natives of a heavily infected trypanosomiasis focus of the Kwango district in Belgian Congo, after they were given 0.002 to 0.003 gm. per kilogram of pentamidine, whereas new infections were discovered in 2.5 per cent of a series of natives used as controls.

Diamidines in Treatment of Other Protozoal Infections. Daubney and Hudson⁹ have reported that stilbamidine is "remarkably effective" in the

treatment of *Babesia canis* infections of dogs, and also noted cures in two instances of *Babesia cabelli* infections (biliary fever) in horses. The observations of Daubney and Hudson were confirmed by Carmichael⁷ who treated 116 dogs infected with babesiasis (tick fever) and concluded that propamidine was the most valuable drug available for this disease. Of their animals 102 were cured with a single dose; 10 relapsed, but were cured with a second dose. Only four of the animals died. Fulton¹² has reported that

TABLE II
Clinical Trials in Diamidines in Trypanosomiasis

Author	Disease Treated	No. of Cases	Drug Used	Results
Harding, ¹⁶ 1940	Nigerian Trypanosomiasis	13	Stilbamidine	Cured 3 Improved 1 Unchanged 1 Worse 8
McLetchie, ²⁶ 1940	Nigerian Trypanosomiasis	14	Stilbamidine	Cured 8 Improved 4 Died 2
Bowesman, ⁶ 1940	Trypanosomiasis	34	Stilbamidine	Improved 28 Unimproved 2 Died 4
Saunders, ²⁹ 1941	Trypanosomiasis	14	Pentamidine	Cured 11 Improved 3
Lawson, ²¹ 1942	Gambian Trypanosomiasis	53	Pentamidine	Cured 41 Improved 7 Unimproved 4 Died 1
Gilbert, ¹⁴ 1943	Trypanosomiasis	14	Pentamidine	Improved 11 Unimproved 1 Died 2

stilbamidine is definitely anti-malarial in cases of *Plasmodium relictum* infections of canaries and against *Plasmodium knowlesi* infections of monkeys.

BACTERICIDAL EFFECTS OF DIAMIDINES

Experimental Studies. In 1942 Fuller¹¹ reported that Gram-positive cocci are killed when exposed to diamidines and noted that the *Streptococcus viridans* is the most sensitive and *Staphylococcus aureus* the least sensitive member of this group. Gram-positive anaerobic bacilli are more resistant than the cocci but more sensitive than Gram-negative bacilli. Of the anaerobes, *Clostridium oedematiens* is most sensitive and *Clostridium welchii* least sensitive. This order of sensitivity of bacteria to diamidines is similar to their sensitivity to sulfonamides.

As a result of these observations, Thrower and Valentine³² carried out in vitro experiments using *Staphylococcus aureus* to test the bacteriostatic properties of propamidine, and reported that against certain strains of

staphylococcus, propamidine was more effective than sulfathiazole. He noted also that the antibacterial effect of the amidines was not inhibited by p-aminobenzoic acid which antagonizes the action of the sulfonamides.

In a typical experiment, sulfathiazole exerted an antibacterial effect in a minimal effective concentration of 1:32,000, whereas propamidine was found to be effective in a minimal concentration of 1:125,000. Preliminary studies showed that against clostridia, propamidine exerted an effect of the same order as against staphylococci.

Antibacterial Effects of Diamidines in Plastic Surgery and in Open Wounds. In the field of plastic surgery, persisting streptococcal infections have not infrequently delayed healing of wounds and have provided a source for cross-infections in wards. These streptococcal infections have been in some instances most difficult to control. In consideration of the antibacterial properties of diamidines as detailed above, Thrower and Valentine³² studied the effects of using propamidine in a jelly base as a dressing for such infected wounds, and reported that under such circumstances this drug was remarkably effective. Wounds which had remained infected for more than a year showed rapid improvement, permitting early skin-grafting or promoting early spontaneous healing. McIndoe and Tilley²⁵ found that 0.1 per cent propamidine in a water-soluble jelly base successfully eradicated similar infections. These workers were particularly impressed by a lack of irritation of the surrounding skin following this treatment. Not all staphylococcal infections were cleared, however, and *B. proteus*, *Pseudomonas*, and *B. subtilis* infections also remained unaffected.

Morley and Bentley²³ reported that propamidine in a soft cream combined with a local anesthetic, controlled streptococcal and staphylococcal infections of burned surfaces. These authors, like McIndoe and Tilley, noted the failure of this drug to control pus producing saprophytes such as *B. proteus*, *Pseudomonas* and *B. subtilis*.

Similar results were observed by Hall and Gross¹⁵ in the treatment of ulcers of the leg, deep infected wounds, and infected burns.

THERAPEUTIC TRIAL OF DIAMIDINES IN RHEUMATOID ARTHRITIS

Although the cause of rheumatoid arthritis remains unknown, a considerable amount of indirect evidence suggests that an infectious agent may be responsible. Since present-day methods of treatment for rheumatoid arthritis are admittedly insufficient, the discovery of a new group of antibacterial chemotherapeutic agents was believed to warrant their trial in patients with this condition.

Because of these considerations, six soldiers suffering with active and progressive rheumatoid arthritis were given a trial of therapy with diamidine derivatives. Four were treated with stilbamidine and two with propamidine. The patients were all males whose ages ranged from 21 to 54 years. The

arthritis had been present for periods ranging from six months to eight years. In all of these patients the disease had appeared insidiously. Each had a polyarticular inflammation which had run a progressive course, and in each patient the progress of the inflammation of joints was continuing. Each patient was crippled to some extent by his articular disease, and the changes which had taken place in the joints were easily detectable on clinical examination. Many of the involved joints had a spindle shaped appearance because of swelling of the joints accompanied by atrophy of the adjacent muscles. Periarticular and synovial thickening were common, and effusions were present in some joints. The roentgenograms showed normal findings where the involvement of joints was recent in onset and in the further advanced stages of the disease showed narrowing of joint spaces, atrophy of epiphyseal bone and in one far advanced instance, marginal lipping.

These six patients manifested more or less severe degrees of systemic disturbances such as loss of weight, some degree of hypochromic anemia and elevation of the erythrocyte sedimentation rate.

The joints were carefully examined before beginning the therapy and the findings of the examiners were filed. At the termination of the courses of therapy each patient was carefully reexamined in regard to the character of the disease in each affected joint. The findings at the beginning and at the end of the therapeutic program were then compared.

Dosage. The diamidines were prepared by solution in buffered, slightly alkaline distilled water. The concentration of the solution was such that each cubic centimeter contained 5 mg. of the drug. Each patient was given two preliminary doses of 5 c.c. (25 mg.) intramuscularly at intervals of three or four days. When it was observed that these intramuscular amounts were well tolerated, the patients were given the drug in doses of 10 c.c. (50 mg.) intravenously on Monday, Wednesday and Friday of each week. The intravenous injections were given slowly; approximately five minutes were required for intravenous injection of 10 c.c. of the solution. Injections were continued until each patient had received a total of one gram of the drug.

Laboratory Studies. The level of hemoglobin, erythrocyte count, leukocyte counts, urinalysis and erythrocyte sedimentation rates were determined at frequent intervals.

Results. The patients did not appear to be benefited in any way. There was no lessening of the degree of swelling or tenderness and no significant alteration in the sedimentation rate, level of hemoglobin or erythrocyte count. Of six patients treated, five stated that they had experienced some degree of subjective improvement of appetite. However, there was no significant gain in body weight.

No toxic reactions were observed.. None of the tests disclosed any significant alteration from the findings which were noted before the administration of the drug.

After administering these drugs for 30 days, and again at the completion

TABLE III
Summary of Clinical Data in Patients with Rheumatoid Arthritis Treated by Diamidines

Case No.	Age	Duration Arthritis Years	Clinical Observations Regarding Joints	Report of Roentgenograms	Hb. R.B.C. Sed. Rate	Activity of Arthritis	Amount of Diamidine and Manner of Administration
1	54	8	Shoulders limited in abduction to 90°. Atrophy of muscles about shoulders. Right elbow swollen and held in 35° flexion. Right wrist swollen and tender. Left elbow swollen and held in 50° flexion. Left wrist swollen, tender and limited in motion. Heads of all metatarsal bones prolapsed.	<i>Rt. Elbow:</i> Proliferation of bone at medial aspect of humero-ulnar joint. Decalcification of bones about elbow joint.	<i>Hb.</i> 12.5 gm. <i>R.B.C.</i> 4.05 mil. <i>Sed. Rate</i> 40 mm./hr.	Severe	July 31, Aug. 3, 1944, 25 mg., I.M. Aug. 5 to Sept. 25, 1944, 50 mg. I.V., 3x weekly Total Stilbamidine 1250 mg.
2	21	6/12	Right sternoclavicular joint swollen and tender. Right elbow swollen and tender, painful on motion. Knees swollen and contained excess fluid.	<i>Rt. Knee:</i> Negative	<i>Hb.</i> 15 gm. <i>R.B.C.</i> 5.28 mil. <i>Sed. Rate</i> 29 mm./hr.	Moderate	June 16 to Sept. 1, 1944, 50 mg. Stilbamidine, I.V. 3x weekly Total 1000 mg.
3	22	9/12	Wrists swollen, tender and painful on motion. Knees swollen, contained excess fluid and painful on motion.	<i>Knees:</i> Negative	<i>Hb.</i> 15 gm. <i>R.B.C.</i> 4.9 mil. <i>Sed. Rate</i> 7 mm./hr.	Severe	June 15 to Sept. 1, 1944, 50 mg. Stilbamidine, I.V. 3x weekly Total 1000 mg.

TABLE III—Continued

Case No.	Age	Duration Arthritis Years	Clinical Observations Regarding Joints	Report of Roentgenograms	Hb. R.B.C. Sed. Rate	Activity of Arthritis	Amount of Diamidine and Manner of Administration
4	35	2	Right elbow swollen, tender and held in 75° flexion and in 105° extension, painful on forced motion. Left elbow swollen, tender, painful on motion and limited in flexion. Proximal interphalangeal joint third finger of right hand swollen and tender. Right knee moderately swollen with excess fluid. Left knee swollen, tender on motion and limited in flexion. Many other joints similarly affected.	Ankles: Negative	Hb. 9 gm. R.B.C. 3.5 mil. Sed. Rate 30 mm./hr.	Severe	June 15 to Sept. 1, 1944, 50 mg. Propamidine, I.V. 3x weekly Total 1000 mg.
5	28	10/12	Elbows swollen and tender. Right knee swollen and contained excess fluid.	Rt. Elbow: Negative	Hb. 12.5 gm. R.B.C. 4.3 mil. Sed. Rate 15 mm./hr.	Severe	June 15 to Aug. 15, 1944, 50 mg. Propamidine, I.V. 3x weekly Total 1000 mg.
6	38	5	Right elbow held in 30° flexion with thickening of synovial membrane. Left elbow swollen and held in 15° flexion. Wrists limited in motion. Proximal interphalangeal joint right second finger swollen, discolored and tender. Metacarpophalangeal joint No. 1 left and interphalangeal joint No. 1 left, swollen, discolored and tender. Metacarpophalangeal joints No. 2 and No. 3 left and the proximal interphalangeal joint No. 3 left, swollen, tender. Quadriceps extensor muscles atrophied. Knees swollen. Right ankle swollen, and tender, and right subastragalar joint limited in motion. Mouth opening limited to 2 cm.	Severe destructive changes involving many joints.	Hb. 10 gm. R.B.C. 4.3 mil. Sed. Rate 52 mm./hr.	Severe	June 15 to Aug. 15, 1944, 50 mg. Stillbamidine, I.V. 3x weekly Total 1000 mg.

TABLE IV
Infections Controllable by Diamidines

Disease	Synonyms	Causative Organism	Animal Affected
Leishmaniasis	Kala-azar Tropical Splenomegaly Dum Dum Fever	<i>Leishmania donovani</i>	Man
Trypanosomiasis	African Sleeping Sickness	<i>Trypanosoma rhodesiense gambiense</i>	Man
Babesiasis	Tick Fever	<i>Babesia canis</i>	Dogs
	Biliary Fever	<i>Babesia cabelli</i>	Horses
Malaria	—	<i>Plasmodium relictum</i>	Canary
	—	<i>Plasmodium knowlesi</i>	Monkey
Wound Infections	—	Streptococci Staphylococci	Man

of the course, renal and hepatic functions were studied by means of phenol-sulfonphthalein tests, and urea clearance tests for renal function, and brom-sulfalein test for liver function. These tests remained normal.

SUMMARY

1. A group of chemical substances consisting of various organic radicals carrying strongly basic amidino groups have been found to be of considerable therapeutic value in the treatment of a number of protozoal and bacterial diseases.

2. These compounds appear to be particularly powerful in their action against human leishmaniasis, a common and exceedingly dangerous disease of the tropics.

3. Less certain but very promising effects have been reported in treatment of human trypanosomiasis.

4. Notable therapeutic value has been demonstrated for these compounds in the treatment of infections of surface wounds such as in burned surfaces, and in wounds associated with plastic surgery.

5. Control of protozoan infestations of dogs and horses with organisms belonging to the genera of *Babesia*, and of malaria in canaries and monkeys has been achieved with these drugs.

6. Patients with rheumatoid arthritis who were submitted to preliminary trials of therapy with diamidines showed no tendency to improvement.

BIBLIOGRAPHY

1. ADAMS, A. R. D.: Studies in chemotherapy. XXVI. A case of Indian kala-azar treated with 4:4' diamidinodiphenoxy pentane, Ann. Trop. Med., 1941, xxxv, 53.

2. ADAMS, A. R. D., and YORKE, W.: Studies in chemotherapy. XXIII. A case of Indian kala-azar treated with 4:4' diamidino stilbene, *Ann. Trop. Med.*, 1939, xxxiii, 323.
3. ADAMS, A. R. D., and YORKE, W.: Studies in chemotherapy. XXV. A second case of Indian kala-azar treated with 4:4' diamidino stilbene, *Ann. Trop. Med.*, 1940, xxxiv, 173.
4. ADLER, S., and TCHERNOMORETZ, I.: The action of 4:4' diamidino stilbene on *Leishmania donovani* in the Syrian hamster, *Circetus auratus*, *Ann. Trop. Med.*, 1939, xxxiii, 313.
5. ADLER, S., and RACHMILEWITZ, M.: A note on the treatment of a case of *Leishmania infantum* with 4:4' diamidino stilbene, *Ann. Trop. Med.*, 1939, xxxiii, 327.
6. BOWESMAN, C.: A short report on the use of 4:4' diamidino stilbene in the treatment of human sleeping sickness, *Ann. Trop. Med.*, 1940, xxxiv, 217.
7. CARMICHAEL, J.: Treatment of canine babesiasis by 4:4' diamidino diphenoxy propane, *Ann. Trop. Med. and Hyg.*, 1941, xxxv, 191.
8. DAUBNEY, R., and HUDSON, J. R.: Action of two aromatic diamidines on *Trypanosoma congolense* infections in cattle with a note on delayed poisoning by 4:4' diamidino diphenoxy pentane, *Ann. Trop. Med.*, 1941, xxxv, 175.
9. DAUBNEY, R., and HUDSON, J. R.: A note on the chemotherapeutic action of 4:4' diamidino stilbene in *Babesia canis* infections of domestic animals, *Ann. Trop. Med. and Hyg.*, 1941, xxxv, 187.
10. DEVINE, J.: Studies in chemotherapy; changes in the blood produced by administration of 4:4' diamidino stilbene, *Ann. Trop. Med.*, 1940, xxxiv, 67.
11. FULLER, A. T.: Antibacterial actions and chemical constitution in long chain aliphatic bases, *Biochem. Jr.*, 1942, xxxvi, 548.
12. FULTON, J. D.: The course of *Plasmodium relictum* infection in canaries and the treatment of bird and monkey malaria with synthetic bases, *Ann. Trop. Med.*, 1940, xxxiv, 53.
13. FULTON, J. D., and YORKE, W.: Increased toxicity of old solutions of stilbamidine, *Ann. Trop. Med.*, 1942, xxxvi, 134.
14. GILBERT, S. W.: Pentamidine in treatment of late cases of sleeping sickness, *Trans. Roy. Soc. Trop. Med. and Hyg.*, 1943, xxxvi, 353.
15. HALL, M. H., and GROSS, CLARA D.: Propamidine at an E. M. S. Hospital, *Lancet*, 1943, i, 140.
16. HARDING, R. D.: A trial with 4:4' diamidino stilbene in the treatment of sleeping sickness at Gadau, Northern Nigeria, *Ann. Trop. Med.*, 1940, xxxiv, 101.
17. HAWKING, F., and SMILES, J.: The distribution of 4:4' diamidino stilbene in trypanosomes and mice as shown by fluorescence, *Ann. Trop. Med.*, 1941, xxxv, 45.
18. HENRY, A. J., and GRINDLEY, D. N.: Fluorescence and absorption of stilbamidine and its estimation in biological fluids, *Ann. Trop. Med.*, 1942, xxxvi, 102.
19. HUMPHREYS, R. M.: Two cases of oral pharyngeal leishmaniasis treated with pentamidine, *Ann. Trop. Med.*, 1942, xxxvi, 9.
20. KIRK, R., and SATI, M. G.: Notes on some cases of Sudan kala-azar treated with 4:4' diamidino stilbene, *Ann. Trop. Med.*, 1940, xxxiv, 83.
21. LAWSON, T. L.: Trypanosomiasis treated with "pentamidine," *Lancet*, 1942, ii, 480.
22. LOURIE, E. M., and YORKE, W.: Studies on chemotherapy. XXI. The trypanocidal action of certain aromatic diamidines, *Ann. Trop. Med.*, 1939, xxxiii, 289.
23. MORLEY, GEORGE H., and BENTLEY, J. P.: Propamidine in burns, *Lancet*, 1943, i, 138.
24. MCCOMAS, G., and MARTIN, N. H.: Trypanosomiasis treated with pentamidine: A fatal case, *Lancet*, 1944, i, 338.
25. MCINDOE, A. H., and TILLEY, A. R.: Propamidine in chronic streptococcal infection of raw surfaces, *Lancet*, 1943, i, 136.
26. MCLEITCHIE, J. L.: The treatment of early cases of Nigerian trypanosomiasis with 4:4' diamidino stilbene, *Ann. Trop. Med.*, 1940, xxxiv, 217.

27. NAPIER, L. E., and SEN GUPTA, P. C.: Diamidino stilbene in the treatment of kala-azar, *Ann. Trop. Med. and Hyg.*, 1941, xliv, 45.
28. NAPIER, L. E., and SEN GUPTA, P. C.: A peculiar neurological sequel to administration of 4:4' diamidino diphenyl ethylene (M & B 744), *Indian Med. Gaz.*, 1942, lxxvii, 71.
29. SAUNDERS, G. F. T.: Preliminary report on the treatment of sleeping sickness by 4:4' diamidino diphenoxy pentane, *Ann. Trop. Med.*, 1941, xxxv, 169.
30. SOMERS, R. B.: Kala-azar treated with 4:4' diamidino stilbene, *Lancet*, 1944, i, 531.
31. SEN GUPTA, P. C.: Observations on the neuropathic sequel of diamidino-stilbene therapy in kala-azar, *Indian Med. Gaz.*, 1943, lxxviii, 537.
32. THROWER, W. R., and VALENTINE, F. C. O.: Propamidine in chronic wound sepsis, *Lancet*, 1943, i, 133.
33. VAN HOOF, L., HENRARD, C., and PEEL, E.: Pentamidine in prevention and treatment of trypanosomiasis, *Trans. Roy. Soc. Trop. Med. and Hyg.*, 1944, xxxvii, 271.
34. WINGFIELD, A. L.: 4:4' diamidino stilbene in the treatment of kala-azar, *Ann. Trop. Med.*, 1941, xxxv, 55.
35. YORKE, W.: Recent work on the chemotherapy of protozoal infections, *Trans. Roy. Soc. Trop. Med. and Hyg.*, 1940, xxxiii, 463.

CASE REPORTS

PNEUMOCOCCIC ARTHRITIS: REPORT OF A CASE TREATED WITH PENICILLIN*

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RECENTLY Boger¹ reported a case of "primary" or "cryptogenic" pneumococcic arthritis cured with sulfadiazine orally and intra-articularly. Boger reviewed the literature and collected 227 cases of pneumococcic arthritis of which 34 were considered "primary." Of these, only four cases were adequately described and can be definitely called "primary" pneumococcic arthritis. We are reporting a case of "primary" pneumococcic arthritis treated with penicillin.

CASE REPORT

C. D., a negro laborer, aged 29, was admitted to the Gallinger Municipal Hospital on January 5, 1944, with the complaint of pain and swelling of the left knee for five days. At that time, upon stepping out of bed, he fell to the floor. He found his left knee was swollen, hot, painful, and unable to bear weight. These symptoms persisted until the time of admission. Two months previously he had struck his right leg with a pick. He was treated at a clinic and was told the bone appeared splintered on the roentgenogram, but only local dressings were applied. This leg remained painful, and weight-bearing was slightly difficult. However, he continued to work until the onset of his present illness. The remainder of his history was negative.

Examination revealed the patient to be well developed and nourished. The left knee was greatly swollen, red, painful, and much distended with fluid. It was held in semi-flexion. The periarticular tissues were edematous, white, and shiny, and the inflammation extended up to the upper one-third of the thigh. The venous circulation was prominent. Slight point tenderness was present over a small scar on the anterior surface of the right leg at the junction of the upper and middle thirds. The temperature was 102° F., pulse 80, respiratory rate 22. The remainder of the physical examination was normal.

A hemogram showed a hemoglobin of 77 per cent, red blood cell count of 3.35 millions and 14,450 leukocytes with 80 per cent neutrophils. Urinalysis was negative. Roentgenograms of the lower extremities revealed marked soft tissue swelling of the left knee with no other abnormalities. Aspiration yielded 90 c.c. of yellow seropurulent material which, on culture, showed Type 12 pneumococci.

The patient was placed on sulfadiazine, 4 grams initially and 1 gram every four hours. Skin traction was applied to the left lower extremity. This therapy was continued for three weeks without clinical improvement, and the cultures from the knee fluid remained positive. In spite of repeated aspirations the knee continued to accumulate large amounts of fluid. The patient's general condition remained good. On the twenty-fourth hospital day, the patient was started on intra-articular penicillin,

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† This study was done prior to Dr. Feffer's entrance into the Armed Forces.

15,000 units daily. These injections were continued for five days without any change in the condition of the knee, although the knee fluid became sterile. Then, 12,500 units were administered twice daily into the joint space. After 10 days of this regime, the knee appeared healed with only slight flexion deformity, which disappeared gradually in a few weeks. The patient returned six months later for an unrelated illness with no evidence of any abnormality of the knee joint.

COMMENT

The features of pneumococcic arthritis are variable. Only one joint is involved in about 75 per cent of cases. Pain, which is always present, varies greatly in intensity and is sudden or insidious in onset. Periarticular involvement may be slight or extensive, and the suppuration may perforate the capsule and extend through all the surrounding tissues into the musculature. It is generally agreed that "primary" pneumococcic arthritis is a metastatic focus of a bacteremia for which the primary site cannot be demonstrated. Although the diagnosis of pneumococcic arthritis should not be made until the pneumococci have been isolated from the joint fluid, several investigators^{2, 3} have reported certain findings which they consider pathognomonic. The periarticular edema is white, the venous collateral circulation prominent, and regional lymphadenopathy is not marked. Joint fluid reaccumulates rapidly after aspiration. The local findings and fever are marked, but the patient's general condition appears good. Our patient demonstrated all these features except that his temperature never exceeded 102° F. Most authors, however, do not believe that there are any symptoms or signs which distinguish pneumococcic from other types of pyogenic arthritis.

Prior to the introduction of chemotherapy and antibiotics, treatment consisted of repeated aspirations, injections of air or irrigation with various antiseptics. Passive movements and physical therapy were used as soon as manipulation was tolerated to prevent wasting of muscles and joint disability. Arthrotomy has generally been abandoned. Immobilization is used only in ankylosing cases. It is difficult to evaluate the effect of treatment since spontaneous recoveries have been reported in three out of the four proved cases of "primary" pneumococcic arthritis. The fourth case reported by Boger recovered on sulfadiazine given orally and intra-articularly. However, sulfadiazine orally was ineffective in our patient. Intra-articular penicillin did effect a cure in 10 days with the use of adequate doses twice daily. Our patient had complete restoration of function. Generally, this has been the experience of other investigators. Disability is usually slight when it does occur.

SUMMARY

A case of "primary" pneumococcic arthritis, cured with intra-articular penicillin is reported. Certain pathognomonic features, previously described, were observed.

BIBLIOGRAPHY

1. BOGER, W. P.: Pneumococcic arthritis. Report of case of so-called primary pneumococcic arthritis, *Jr. Am. Med. Assoc.*, 1944, cxxvi, 1062.
2. PLISSON and BROUSSE: Arthrite purulente primitive à pneumocoques du genou chez l'adulte, *Lyon chir.*, 1920, xvii, 705.
3. CHANTEMESSE, MOCAIGNE and CHIPAULT: Cited by Plisson and Brousse.²

SUBENDOCARDIAL MYOCARDIAL INFARCT*

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THIS is a report of a case of extensive subendocardial myocardial infarction involving the interventricular septum and the anterior wall of the left ventricle. There was no coronary occlusion, and the electrocardiogram showed no evidence suggestive of a recent myocardial infarct. The rarity of this condition warrants a case report.

CASE REPORT

An 82 year old white female‡ was admitted for the first time after she had collapsed following the extraction of two teeth. Diabetes mellitus was diagnosed at that time, and the Wassermann and Kahn reactions were found to be positive (4 plus). After six days of treatment with insulin and diet the patient was discharged with the diabetes improved. About one year later she was re-admitted following an injury to the left foot complicated by dry gangrene of the fourth left toe. During her stay at home the patient had not taken any insulin, and she had followed her diet inadequately. The family history disclosed that one brother died at the age of 69 of coronary thrombosis. She was gravida VI, para II, with three premature births and one still-birth, and two live children. On admission her chief complaints were pain and swelling of the left foot and some frequency in urination, urgency and incontinence without dysuria. Physical examination revealed a well-developed, well-nourished white woman, resting comfortably in bed. The temperature was 98.6° F., the pulse was 88 per minute, the rhythm was regular. Respirations were 20 per minute, arterial blood pressure was 168 mm. Hg systolic and 70 mm. diastolic. The heart was enlarged to the left, reaching the anterior axillary line in the fifth intercostal space. A high pitched systolic murmur was heard at the apex and the aortic second sound was louder than the pulmonic. The fourth toe of the left foot was bluish-black, and there was reddening and swelling of the dorsum of the foot. The pulse of the left dorsalis pedis artery was not palpable. The clinical diagnosis was gangrene of the left fourth toe and generalized arteriosclerosis. The hemoglobin was 10.4 gm., the erythrocyte count was 4,660,000 per cubic mm. and the leukocytes were 14,300 per cubic mm. with a normal differential count. The fasting blood sugar was 250 mg. per cent, and the non-protein nitrogen was 40 mg. per cent. Twenty-four hour catheterized urine specimen showed an acid reaction, specific gravity 1.013, sugar and tests for acetone were negative. The sediment showed three to five white cells. Roentgenogram of the left foot revealed a fracture to the base of the fifth metatarsus.

The patient was placed on a diabetic diet, received acetylsalicylic acid and sulfadiazine (gm. 1, every 4 hours). Local heat and moist application produced some local improvement.

The temperature ranged between 98.6° and 100° F., and her general condition was good for five days when the temperature rose to 101° F. without elevation of the respiratory or pulse rate. Twenty-four hours later, on the sixth night after admission, the patient suddenly became very restless, had an emesis and an involuntary bowel

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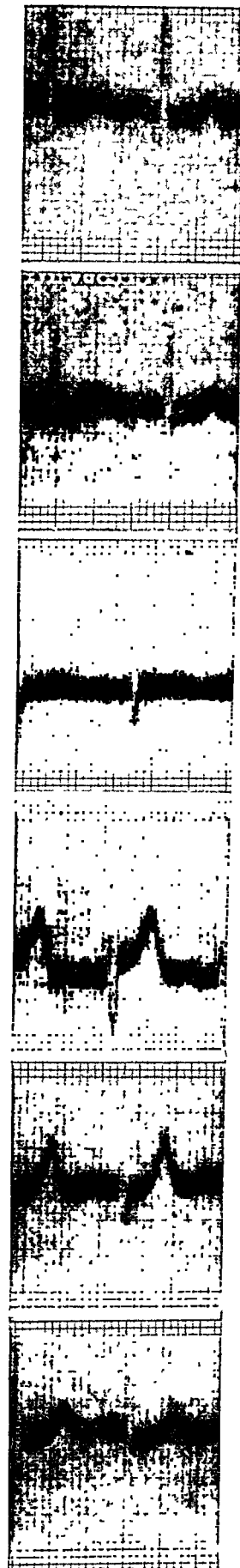


FIG. 1.

movement. She developed marked dyspnea, râles were heard over the lungs and mucus accumulated in her throat. The blood pressure at the beginning of this episode was 116 mm. Hg systolic and 60 mm. diastolic and slowly dropped to 100 mm. Hg systolic and 60 mm. diastolic. The pulse was of fairly good quality and regular, with a rate of 100 to 110. The patient vomited twice more. The impression was that this attack was caused by an acute coronary occlusion. The possibility of a pulmonary embolus was also considered. Oxygen, aminophyllin and morphine sulfate were administered, and the patient improved. Urine examination at that time revealed 4 plus sugar but no acetone; the vomitus showed a 4 plus occult blood. The electrocardiogram taken 17 hours after the beginning of the attack disclosed a definitely abnormal curve with left ventricular preponderance, and no evidence of a recent myocardial infarct. The patient was comfortable and in good condition for 36 hours following the attack, then suddenly she started to gasp for breath, became pale and



FIG. 2. Subendocardial myocardial infarct. Note the recent infarct and the narrow rim of normal myocardium immediately adjacent to the endocardium.

unconscious. The pulse became weak and rapid, the skin cold and clammy and the patient died 10 minutes later.

Necropsy. An autopsy performed six hours after death disclosed the following findings: Severe generalized arteriosclerosis, nephrosclerosis of the arteriolar variety, moderate hypertrophy of the heart, severe coronary arteriosclerosis with narrowing of branches of the left coronary artery in many places, a recent subendocardial myocardial infarct of the left ventricular wall, edema and hyperemia of the lungs, bilateral hydrothorax, chronic passive hyperemia of liver and spleen, moderate fibrosis of the pancreas, multiple myofibromata of the uterus, multiple minute adenomata of the kidneys and early "cytotoxic" contraction of the suprarenals. There was no gross or microscopic evidence of lesions attributable to syphilis.

The gross description of the heart was as follows: The heart was moderately enlarged, especially in its left portion, and weighed 400 gm. The subepicardial fat

was normal. The chambers and endocardium were normal. The tricuspid, pulmonic, aortic and mitral rings measured respectively: 10.0, 7.2, 7.0, and 8.0 cm. in circumference. The tricuspid and mitral leaflets and the aortic cusps exhibited a slight sclerotic thickening. Within the base of the aortic and the mitral rings were a few calcific areas which extended to the septum membranaceum. The myocardium was red-brown. The right ventricular wall measured up to 0.4 cm., and the left up to 1.7 cm. in thickness. The upper portion of the interventricular septum presented a soft, yellowish-red area on its left ventricular aspect. On section, numerous sub-endocardial hemorrhages and yellowish brown areas were noted throughout the septum extending into the anterior wall of the left ventricle and into the anterior papillary muscle. The coronary ostia were narrowed by calcific aortic plaques. The right ostium was abnormally low and covered by the aortic cusp. The arteries had a normal distribution. The left one presented a very severe sclerosis and atheromatosis throughout with a marked narrowing of the lumen of its various branches at several points. The right coronary artery showed much less severe sclerosis. Neither recent nor old occlusions were noted in the main branches. The aorta was rigid, calcified throughout.

The microscopic examination of the myocardium showed in the interventricular septum many large areas adjacent to the endocardium of the left ventricle in which the muscle fibers had a smudgy appearance and stained very poorly. Between the muscle fibers were numerous polymorphonuclear leukocytes and lymphocytes and some extravasated red blood corpuscles. The separation between the infarcted and normal muscle was clear cut (figure 2). Areas of recent infarction were also seen in the anterior wall of the left ventricle and in the left anterior papillary muscle.

The infarct was judged to be between 24 and 36 hours old.¹ The remaining myocardium exhibited a moderate degree of interstitial fibrosis and some thickening of the wall of the arteries.

DISCUSSION

This case is interesting because of the presence of an extensive subendocardial infarct involving about two-fifths of the thickness of the left ventricular wall without any recent or old occlusion of the coronary arteries, although the mouths of both coronary arteries were narrowed and the branches of the coronary arteries were sclerotic, of the "pipe-stem" type, presenting numerous narrowings. Physiologically, therefore, there was doubtlessly chronic coronary insufficiency. This insufficiency was probably increased by the presence of arteriosclerotic plaques in the aorta at the mouths of the coronary arteries. A moderate degree of interstitial fibrosis of the myocardium was the only evidence of this chronic coronary insufficiency which must have been present for a number of years. On this basis, and in connection with the presence of an infectious process, the patient developed left heart failure. This, in time, caused slowing of the circulation for which the severely diseased coronary arteries could not compensate and precipitated acute ischemia of the myocardium leading to infarction. Anatomically, this was an extensive confluent subendocardial infarction. The myocardium did not present the picture of focal necrosis which has been frequently described in cases of chronic coronary insufficiency.

In this instance the clinical picture, aside from the absence of pain, was characteristic of myocardial infarct. The electrocardiogram was definitely abnormal, showing a left ventricular preponderance pattern but no changes characteristic of infarct (figure 1).

It is now recognized that concordant S-T elevation in the limb leads or at least the absence of discordant S-T depression is typical of pericarditis due to the involvement of the subepicardial myocardium. Recently the reverse has been suggested as a sign of subendocardial infarction; viz. concordant S-T depression in the limb leads, at least the absence of discordant S-T elevation.² On this basis the possibility of a subendocardial infarction might have been considered in this case. The S-T depression in Leads I and II can be considered as indicative of the subendocardial infarction found at necropsy. However, the pattern in this case is not convincing because it might have been produced by left heart strain.

It is amazing that so extensive an infarction could occur in this patient without closure of the artery supplying the area. More interesting is the fact that with so extensive an infarct only the inner layer of the myocardium of the left ventricle was involved. The blood flow on the inner side of the left ventricle is closer to the critical level at which infarction occurs than that of the outer side. This lends support to the concept that during systole the extravascular compression of the coronary vessels increases from the epicardial to the endocardial aspect.³ The threshold for infarction would therefore be reached with less diminution in coronary flow on the inner aspect.

The most common sites of subendocardial infarcts are the interventricular septum and the papillary muscles of the left ventricle. These areas are farthest away from large coronary branches. A large septal branch was observed by Schlesinger only in a small percentage of human hearts.^{4, 5} A second factor is the particular exposure of these regions to intraventricular pressure.

Since the exacerbation of the coronary insufficiency was due to failure of the heart, it is possible that therapy directed to improve the failure might have prevented the fatal outcome. Digitalis is a drug which might have accomplished this.

SUMMARY

A case of extensive subendocardial septal myocardial infarction, occurring without occlusion of the coronary arteries, is presented.

The pathogenesis of this unusual condition and the rationale of therapy are briefly discussed.

The authors are indebted to Drs. O. Saphir and L. N. Katz for their advice.

BIBLIOGRAPHY

1. MALLORY, G. K., WHITE, P. D., and SALCEDO-SALGAR, J.: The speed of healing of myocardial infarction, *Am. Heart Jr.*, 1939, xviii, 647-672.
2. LANGENDORF, R., and KOVITZ, B.: Acute myocardial infarction without deviation of the S-T segment of the electrocardiogram, *Am. Jr. Med. Sci.*, 1942, cciv, 239-246.
3. JOHNSON, R. J., and DiPALMA, J. R.: Intramyocardial pressure and its relation to aortic blood pressure, *Am. Jr. Physiol.*, 1939, cxxv, 234-243.
4. SCHLESINGER, M. J., and ZOLL, P. M.: Incidence and localization of coronary artery occlusion, *Arch. Path.*, 1941, xxxii, 178-188.
5. BLUMGART, H. L., GILLIGAN, D. R., and SCHLESINGER, M. J.: Experimental studies on the effect of temporary occlusion of coronary arteries. II. The production of myocardial infarction, *Am. Heart Jr.*, 1941, xxii, 374-389.

RUPTURE OF THE SPLEEN DUE TO TULAREMIA: REPORT OF A CASE*

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INTRODUCTION

RUPTURE of the spleen as one of the manifestations or complications of tularemia apparently has rarely if ever before been encountered. A thorough search of the literature reveals no recorded instance of this nature. A patient was recently observed at Vanderbilt University Hospital in whom this condition was found at autopsy following a clinical course in which the exact diagnosis remained obscure. Because of its unusual nature a report of this case seems justified.

CASE REPORT

History. A 41 year old white male farmer was admitted to the medical service of Vanderbilt University Hospital on December 18, 1944 with a chief complaint of abdominal pain of 17 hours' duration.

Throughout the seven years preceding admission he had typical peptic ulcer symptoms which were treated at home by his local physician. Two years before admission he had an episode of massive hematemesis, and was in bed for one month. At this time a duodenal ulcer was demonstrated by roentgen-ray examination. Following this, and until the present illness he had only occasional epigastric distress, which was relieved by alkalies.

Eighteen days prior to admission the patient went rabbit hunting. He killed and dressed several rabbits, none of which appeared sick. Sixteen days before admission he noticed a small "pimple" on the middle finger of the right hand. His wife removed a scab from this lesion, which progressed in size. Fourteen days before admission the patient had pain in the right shoulder, noticed tender "lumps" in the right epitrochlear region and in the right axilla. The same day he had a rather sudden onset of malaise, followed by a shaking chill, high fever, and drenching sweat. At this time, Dr. David Strayhorn of Nashville was consulted, and a diagnosis of tularemia was made. Serum agglutination against *Pasteurella tularensis* at this time was reported as negative. The patient improved somewhat on bed rest and sedation.

The day before admission to the hospital, following a light meal, he developed dull aching non-radiating pain in the epigastric region associated with nausea and a feeling of fullness. Several hours later he was given an enema which was effective. There was no blood or tarry material in the stool. Immediately following the enema, the patient suddenly felt very faint and perspired freely, but did not lose consciousness. His wife noticed that he had become very pale within the space of a few hours. He remained weak, with some fever and profuse sweats, aching epigastric pain, a feeling of fullness, and nausea without vomiting.

The remainder of the history was non-contributory.

Physical examination on admission. His temperature was 97° F., pulse 120, respirations 40, and blood pressure 70 mm. Hg systolic and 40 mm. diastolic.

General appearance: The patient was a well developed, white male lying motion-

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less, appearing acutely ill with narrowed field of consciousness and presenting the picture of peripheral vascular collapse. The skin was extremely pale and covered with beads of clammy perspiration. The pulse was rapid and thready with a blood pressure of 70 mm. Hg systolic and 40 mm. diastolic.

On the dorsal surface of the proximal interphalangeal joint of the right third finger was a red, raised, non-tender encrusted ulcer about 5 mm. in diameter. An enlarged, slightly tender, right epitrochlear node, and two slightly tender, firm, axillary nodes, each about 3 cm. in diameter were palpable. There was no generalized glandular enlargement. The conjunctivae and buccal mucous membrane were extremely pale. The lungs were clear to percussion and auscultation. Examination of the abdomen revealed diffuse tenderness in the epigastrium and moderate upper abdominal distention. There were spasm and rigidity of the recti in the epigastrium. No organs or masses were felt. Peristaltic sounds were diminished.

Laboratory studies on admission. The red blood cell count was 2,440,000. The white blood cell count was 23,900 and the hemoglobin was 8 grams per cent. The smear showed 83 per cent polymorphonuclear cells, 2.5 per cent stab forms, 13 per cent lymphocytes, and 0.5 per cent monocytes. The non-protein nitrogen was 60 mg. per cent. The total serum protein was 5.80 grams per cent with 3.45 grams of albumin and 2.35 grams of globulin. The erythrocyte sedimentation rate was 42 mm. per hour corrected. The reticulocyte count was 4.4 per cent and the icterus index was 5. Serum agglutination for *P. tularensis* was negative. The urine was clear yellow with a specific gravity of 1.020, and pH of 5. It contained a moderate amount of albumin and a trace of sugar. Microscopic examination of the urine sediment was negative.

Course in the hospital. It was evident on admission that the patient was in a state of shock due to blood loss, and 500 c.c. of pooled plasma were given immediately after arrival on the hospital ward. Throughout the first hospital day the patient was given parenteral fluids and morphine sulfate. The impression at this time was that the patient had tularemia and as a complicating factor had bled profusely from an activated duodenal ulcer. The following day the patient's temperature had risen to 103.6° F., and the white cell count had dropped to 10,500 with an erythrocyte count of 1,100,000 and a hemoglobin of 5.5 gm. A transfusion of 500 c.c. of whole blood was given on the second hospital day.

The patient's abdomen had become much more distended and the tenderness less. Because of the marked abdominal distention and probable paralytic ileus, the question of perforation of the duodenal ulcer arose. Surgical consultation was obtained; it was felt at this time that the signs of peritoneal irritation were not of a degree to warrant the diagnosis of perforation. On the second day the non-protein nitrogen was 63. As there was no evidence of renal insufficiency, this was explained on the basis of blood in the gastrointestinal tract. Because of the continued abdominal distention, the following day a stomach tube was passed and connected to the Wangensteen suction apparatus. A rectal tube was inserted and prostigmine was given several times, with only slight relief of the distention. The Wangensteen suction brought back bile from the stomach, but no blood. The patient had had no bowel movement since admission and confirmatory evidence of bleeding into the gastrointestinal tract was still lacking. A small tap water enema was given without effect.

On the afternoon of the third hospital day the patient suddenly became dyspneic and three hours later there was dullness over the right chest extending in the mid-axillary line from the level of the third interspace down to the base with fine moist râles throughout this area and in the right base posteriorly. Breath sounds were diminished. The respiratory rate was 40. It was felt at this time that the patient had developed tularemic pneumonia. A roentgenogram of the chest showed "an irregular pneumonia involving most of the right lung, somewhat deeply located. The left lung shows a moderately increased bronchovascular shadow with a little thicken-

ing around the left hilus. This is a pneumonia on the right and might well be tularemic pneumonia" (figure 1). Pneumococci, type XIII, were isolated in almost pure culture from the sputum. Because of this and as no laboratory evidence had been confirmatory of the diagnosis of tularemia, it was felt that treatment would have to be directed toward pneumococcic pneumonia, though the impression remained that the pneumonia was on the basis of tularemia. Consequently the patient was given penicillin, 15,000 Oxford units intramuscularly every three hours until the time of death. Following the development of pneumonia, a thoracentesis was done on the right side with the aspiration of 30 c.c. of dark, grossly bloody fluid which did not clot.

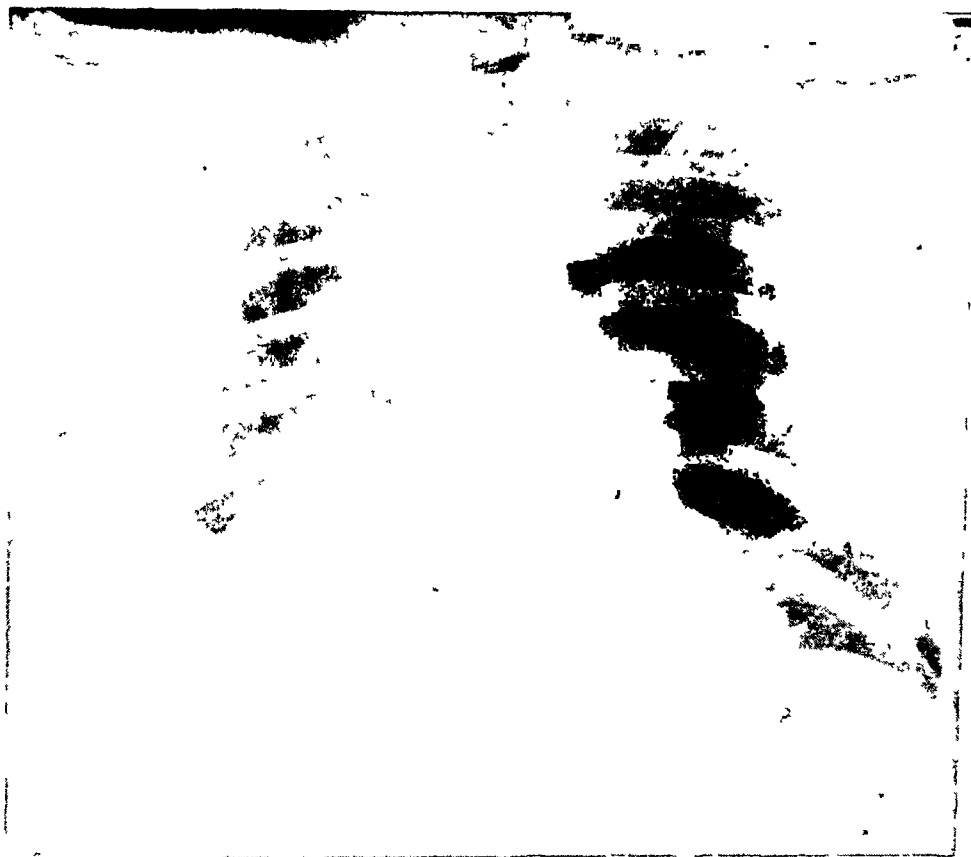


FIG. 1. Roentgenogram showing pulmonary infiltration due to tularemia.

On the third hospital day the patient received another transfusion of 500 c.c. of whole blood. The patient appeared definitely worse with the temperature remaining elevated to 104° F., and a white blood cell count of 10,500. Thoracentesis was again attempted on the right, but no fluid was obtained.

The following day, as the patient still had had no bowel movement and the distention persisted, an enema was given which was effective. The stool was yellowish brown, and the guaiac test for occult blood was negative. It was felt at this time that the patient had bled into the peritoneal cavity, but no signs of fluid intraperitoneally could be elicited. Exploratory laparotomy was considered, but was deemed unwise. Because of the marked abdominal distention, palpation of the abdomen was unsatisfactory. On the fourth hospital day the patient was given another transfusion of 500

c.c. of whole blood, following which the erythrocyte count was 3,440,000 and the hemoglobin 11.4 grams.

On the fifth hospital day the patient presented a typhoidal mental state with hallucinations and confused, incoherent talk. He appeared gravely ill, but was in no pain. On this day for the first time signs of free fluid in the peritoneal cavity were present though difficult to demonstrate because of the abdominal distention which had become worse. The pneumonia had extended upward in the right lung, and on the left there were numerous moist râles at the base posteriorly.

On the sixth hospital day the patient's condition rapidly became worse. He was markedly dyspneic, semi-comatose, and died a few hours thereafter. At the time of the patient's death there was still no laboratory evidence to support the diagnosis of tularemia. By the day following death the cultures of the pleural fluid obtained on the third hospital day had yielded growth of *P. tularensis*. Throughout the course of the illness no positive agglutination for *P. tularensis* was obtained.

Autopsy findings. The significant findings were as follows:

Peritoneal cavity: The peritoneal cavity contained about four liters of dark brownish-red fluid. This lay free and unclotted. In the upper abdomen was gelatinous, dark-red clotted blood which was loosely attached to the stomach, omentum and transverse colon. Although the serosal surfaces were edematous and slightly icteric, there was no evidence of purulent exudate. Further exploration of the upper abdomen revealed a large, swollen, pale liver. Beneath its capsule were a few extremely minute yellowish-gray opacities. These were less than 1 mm. in diameter and barely visible. It was apparent that the liver had been displaced to the right by a large bloody mass which lay in the left upper quadrant. Much of this was fresh, dark red, easily removed elastic clot. When this was stripped away, the rounded edge of the spleen became visible. The thin tense capsule was torn in several places. The splenic vein was exposed and traced to the splenic hilum. During this procedure the spleen was rotated in order to expose the hilum. In attempting to remove the spleen the organ was found to be torn almost in half. The spleen and the associated hematoma weighed 1,000 grams. The anterior half consisted of tense, thin capsule, torn in several areas, which covered gelatinous, dark red blood clot. No splenic tissue was seen in this portion. The posterior portion consisted of spleen, freshly clotted blood, and a laminated, friable, gray and red blood clot. Most of the hemorrhage had occurred between the pulp and the capsule so that there was an enormous subcapsular hematoma which had torn the capsule. The pulp itself was rather soft and pink. Within it one could see the chalky opacities so characteristic of tularemia (figure 2).

Pleural cavities: Each pleural cavity contained about 100 c.c. of blood-tinged unclotted fluid, which contained no fibrin. A few ecchymoses were seen near the pleuro-pericardial reflection.

Lungs: There was moderate atelectasis in each lung. Before they were removed a raised area 2 cm. in diameter in the right middle lobe was seen. Its edges were sharply circumscribed, and on the dull overlying pleura were a few strands of fibrin. This lesion was very firm and unyielding in consistency, and was near the tip of the middle lobe. Two similar lesions were seen in the right lower lobe. Another was felt in the left lower lobe near the medial border. Sections of these lesions had the general shape of infarcts. Their surfaces were raised and dry. Scattered throughout them were yellow opacities about 1 or 2 mm. in diameter. There was some clustering of these to form much larger opaque masses (figure 3). Aside from these specific lesions the lungs showed only atelectasis. There were no areas of ordinary pneumonia. The bronchi contained small quantities of mucus. The larger pulmonary arteries and veins were not remarkable. There was considerable enlargement of the tracheobronchial nodes on each side. They were swollen and moist, and on cut

section a few questionable opacities which suggested necrosis were seen, but the major portion of the cut surface appeared quite moist, and almost gelatinous.

Gastrointestinal tract: No ulcer or scar was seen either in the stomach or duodenum.

Liver: The organ weighed 2150 grams. It was swollen and pale. Through the thin opalescent capsule the minute opacities already described were visible. Cut sections revealed a pale, lusterless, yellowish-tan parenchyma with prominent central veins. Here also a few opaque yellow areas of necrosis were seen.

Microscopic notes. The spleen and liver showed the characteristic areas of focal necrosis seen in tularemia. The lesions in the liver were in the process of resolution. Most of the necrotic debris had been removed in some of the lesions, and there was

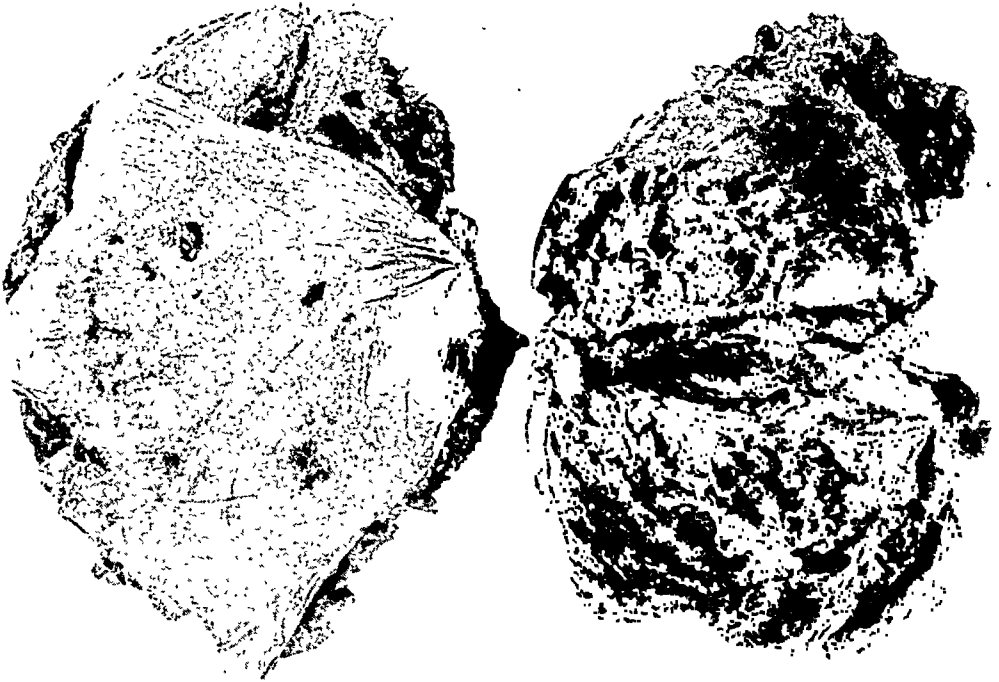


FIG. 2. Photograph of ruptured spleen showing anterior and posterior portions. See text.

definite evidence of fibrosis. There was no artery in the sections of spleen which might have served as the site of initial hemorrhage.

The pulmonary lesions were also characteristic of tularemia, but they were of such a complex nature that they will be described in a separate paper.

Bacteriological findings. Four mice were inoculated intraperitoneally with 0.1 c.c. of emulsified splenic tissue. All of the mice became sick and died on the fourth day. Autopsy revealed markedly enlarged spleens which were studded with large, opaque, yellowish areas. Smears from this tissue stained by Wright's method showed innumerable intracellular short bacillary forms crowding the cytoplasm of large mononuclears. The bacilli were gram-negative. On cystine-dextrose-blood agar slants inoculated with particles of mouse spleen soft gray colonies of small gram-negative bacilli appeared in 48 hours. No growth was obtained on cystine-free blood agar. The microorganisms were agglutinated to titer in known anti-tularensis agglutinating serum.

Pleural fluid, aspirated three days before death of the patient, cultured on cystine-dextrose-blood agar was positive for *P. tularensis* on the following fourth day or one day after the patient's death. These microorganisms also agglutinated to titer in known anti-tularensis agglutinating serum.

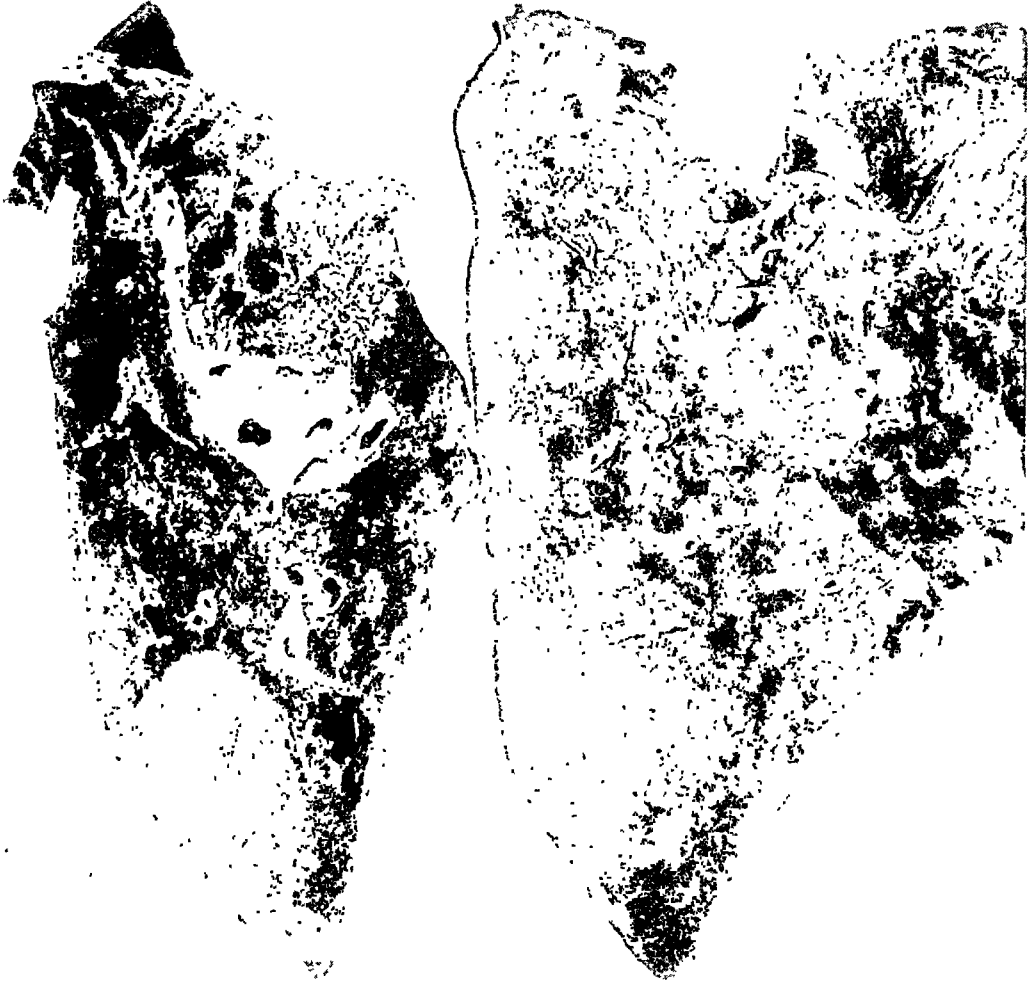


FIG. 3. Photograph of cut section of right lung showing characteristic gross lesions of tularemia.

COMMENT

The diagnostic problem in this patient was rendered difficult by the fact that a hemorrhagic crisis occurred during the course of the illness. Although no direct evidence for gastrointestinal hemorrhage could be elicited, neither could

completely valid reasons be obtained for supporting a diagnosis of massive intra-peritoneal hemorrhage. The reliable evidence of a previous and possible persistence of a peptic ulcer added to the difficulty. Nevertheless, the history of handling wild rabbits and the development of the ulcero-glandular disease with subsequent pulmonary involvement presented almost adequate evidence for tularemia in spite of the absence of laboratory confirmation in the form of agglutinating antibodies against *P. tularensis*. Although in most instances these antibodies can be demonstrated in the third week of the disease, cases in which agglutinins cannot be demonstrated at this time are encountered.^{1, 2} Positive culture from the pleural exudate grew out too late in this case to support the clinical diagnosis of tularemia.

The pathogenesis of massive intrasplenic hemorrhage with subsequent splenic rupture in this instance although unusual, can nevertheless be postulated if the behavior of *P. tularensis* in the disseminated disease is considered.³ The focal areas of necrosis in various tissues and organs apparently have their origin as miliary intracapillary or perivascular areas of inflammatory reaction initiated by the presence of the microorganisms in these environments favorable to their proliferation.⁴ Rapid focal destruction of tissue can and does involve vascular walls as evidenced by hemorrhage and thrombosis in areas involved by the infection.⁴ That larger vessels such as intrasplenic veins may become involved in a focal destructive process of this type is not surprising; in fact, it is perhaps more surprising that such circumstances do not occur more frequently. Once a larger vessel wall has been broken down by this process, the subsequent hemorrhage into and resulting rupture of the spleen can be readily envisaged.

The gross pathological features in the lungs and liver in this case were characteristic of those found in tularemia.^{5, 6} The peripherally located, sharply circumscribed, firm, infarct-like areas of pulmonary inflammatory reaction may be considered as almost pathognomonic, as are the yellow or chalk-like areas of necrosis in the liver and spleen nearly always associated with this disease.

Since there seems to be every reason to believe that an occurrence of this type may develop in other cases of tularemia this detailed report has been made. The symptoms attendant upon this complication may present many confusing problems unless the possibility of its occurrence is considered.

SUMMARY

1. The clinical and postmortem features of a case of splenic rupture due to tularemia are described. A survey of the literature reveals no similar previously reported case.

2. The pathologic features of the pulmonary lesions in this case at autopsy were so characteristic of tularemia that a gross diagnosis of the disease could be established before laboratory confirmation by isolation and identification of the microorganism was possible.

BIBLIOGRAPHY

1. RANSMEIER, J. C., and EWING, C. L.: The agglutination reaction in tularemia, Jr. *Infect. Dis.*, 1941, lxix, 193-205.
2. KENNEDY, J. A.: Pulmonary tularemia, Jr. *Am. Med. Assoc.*, 1942, cxviii, 781-787.

3. FOSHAY, L.: Tularemia: A summary of certain aspects of the disease including methods for early diagnosis and the results of serum treatment in 600 patients, *Medicine*, 1940, xix, 1-83.
4. GOODPASTURE, E. W., and HOUSE, S. J.: The pathologic anatomy of tularemia in man, *Am. Jr. Path.*, 1928, iv, 213-226.
5. FRANCIS, EDWARD, et al.: The pathology of tularemia, *Natl. Inst. Health, Bull. No. 167*, 1937, Washington.
6. Intrathoracic changes in tularemia, *Med. Bull. Vet. Admin.*, 1934, xi, 77-83.

DISSEMINATE LUPUS ERYTHEMATOSUS UNSUCCESSFULLY TREATED WITH PENICILLIN, ROENTGEN-RAY CASTRATION AND SERUM ALBUMIN *

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DISSEMINATE lupus erythematosus is a systemic disease which may be acute, subacute or chronic. Manifestations are commonly found in the skin, joints and viscera. Sixty to 80 per cent of the cases of the disseminate form occur in females during the second and third decades of life.¹ The mortality rate in the subacute form is about 50 per cent, whereas in the acute form it is reported as invariably fatal.² The etiology and pathogenesis of this disorder are still unknown. Stokes and associates³ have attempted to integrate the variegated manifestation of lupus erythematosus on an infection-allergy basis with major involvement of the vascular system and the skin. Klemperer and associates⁴ have suggested that the primary pathologic lesion of the disorder is located in the connective tissue systems of the body, expressing itself as a fibrinoid degeneration of the collagenous fibers probably due to physio-chemical changes in the colloidal state of the connective tissue. No specific therapy has been found.

The following case report is that of typical subacute disseminate lupus erythematosus unsuccessfully treated with penicillin and roentgen castration.

CASE REPORT

The patient was a 32 year old Negro female, who was in good health until June 1944, at which time she complained of vague, intermittent low back pain. There was no history of unusual exposure to sunlight nor of photosensitivity. In July 1944 she observed the appearance of symmetrical erythematous lesions on both elbows, and later a similar erythematous patch that was of a butterfly pattern which bridged the nose and tended to spread toward the malar eminences. Concomitantly, a similar rash appeared on the scalp which eventually became scaly with associated falling of the hair. In September 1944 she noted occasional facial edema and slight puffiness of the eyelids upon arising each morning and a few weeks later, slight intermittent pedal edema, more pronounced at night. About this time there appeared a generalized lymphadenopathy; the largest nodes, about 1.5 cm. in diameter, were present in the cervical areas. They were firm, freely movable and non-tender. Other physical findings were not significant at the time of this examination in October. Hematological studies showed a normal hemogram and normal blood chemistry (see table). The corrected sedi-

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mentation rate was 3 mm. in one hour. Urinalysis and blood Wassermann reaction were negative.

TABLE I
Hemogram and Blood Chemistry during Course of Disease

Date	R. B. C. (Millions)	W. B. C.	Sed. Rate per Hr. Corrected	Tot. Pro- tein gm. %	A/G ratio	N.P.N.	Creatinine
11-16-44	4.22	6,400	3 mm.	6.1	1.65	29	
1-6-45	3.50		10 mm.	5.0			
2-18-45				4.43	0.98	43	1.8
2-21-45	3.90	7,600					
3-7-45	2.60	11,300		5.38	0.46	95	3.0
3-10-45						127	2.7
3-12-45				4.59	0.93	219	6.0
3-15-45				4.93	0.88	92	3.0
3-19-45				4.72	1.42	98	
3-22-45				5.01		96	1.6
3-29-45	2.80	13,800		4.19	1.40	115	4
4-1-45	2.56	18,050	21 mm.*				
4-2-45				4.84	0.99	121	5

* Uncorrected.

In November 1944 the patient developed slight tenderness in the right upper quadrant and an enlarged liver, three fingers' breadth below the right costal margin. At this time her temperature ranged from 99° to 101° F. The only new complaints were intermittent arthritic pains in the shoulder, wrists, elbows and fingers, migratory in nature. A biopsy of one of the largest lymph nodes showed only lymphoid hyperplasia, not conforming to any definite pathologic pattern. Also, a biopsy of one of the skin lesions showed no diagnostic changes. The patient was given 500,000 units of penicillin intramuscularly, 20,000 units every four hours with no change in her condition. In addition, she was given blood transfusions, thiamine hydrochloride, and crude liver extract.

In December, she developed a left pleural effusion. The liver extended about four fingers' breadth below the costal margin and there was a slight amount of abdominal fluid. She developed a persistent anorexia and nausea.

During January and February 1945 the patient was studied by Dr. Edward Rose at the University of Pennsylvania Hospital, who confirmed the diagnosis of disseminate lupus erythematosus.

In addition to supportive therapy, the treatment there consisted of a course of iodides and roentgen-ray castration. The castration therapy was instituted because of previous observations by Rose and Pillsbury⁵ suggesting a possible relationship between ovarian function and lupus erythematosus. The skin lesions showed some improvement under the iodide therapy, but there was progression in the systemic manifestations including anemia, hypoproteinemia and evidence of renal involvement. At this time she showed casts in the urine, proteinuria and microscopic hematuria.

The patient was readmitted to Freedmen's Hospital, February 18, 1945 at which time she showed generalized edema, anemia (see table) and dyspnea. There were signs of bilateral pleural effusion and ascites. The scalp lesions had resulted in several areas of alopecia. Because of the severe hypoproteinemia—4.43 grams per 100 c.c.; A/G ratio of 0.98—she was given serum albumin. A total of 400 grams was given during a period of 16 days beginning March 10, 1945. A slight rise both in the total protein and the A.G. ratio occurred but without change in the edema or effusions. An attempt to produce diuresis by mercupurin and ammonium chloride was

made. Two ampules of mercupurin in 20 c.c. of distilled water were given intravenously on Feb. 25, March 2, and March 5, 1945, while the patient was taking 4 gm. of ammonium chloride daily. No diuresis occurred. The significant change which did occur was an increase in nitrogen retention (see table).

The course in the hospital was gradually downward. Her temperature ranged from 100° to 101° F. A blood culture on March 7, 1945 was negative. About March 15, 1945 the patient developed a sore throat which became more severe. This was treated unsuccessfully with sulfadiazine. On March 27, 1945 a blood culture positive for *Staphylococcus aureus* was obtained. At this time she developed a transitory pleuropericardial friction rub. The patient died in uremia April 3, 1945, approximately 10 months after onset of initial symptoms. Postmortem examination could not be obtained.

SUMMARY

A typical fatal case of subacute disseminate lupus erythematosus is presented. The total duration of illness was about 10 months. The initial lesion developed on the skin, and later clinical signs of involvement of the joints, pleura, liver and kidneys were present. A gradually progressive hypoproteinemia developed with associated generalized edema, ascites, and pleural effusion. No clinical improvement resulted from the administration of 400 grams of serum albumin during a

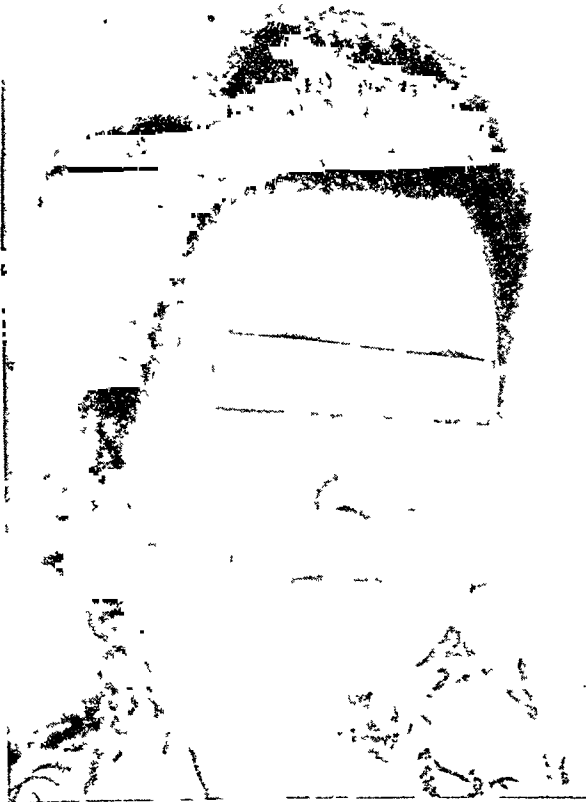


FIG. 1. Photograph showing symmetrical erythematous lesions of the nose and cheeks.

period of 16 days. The anemia was progressive, leukocytosis was present only during the last month of illness, a low grade fever was constant but the sedimentation rate was not elevated. Penicillin and roentgen castration gave no beneficial effect. Several days after mercupurin intravenously the non-protein nitrogen became elevated. There was some subsequent drop in the non-protein nitrogen but not to normal. The patient died in uremia.

BIBLIOGRAPHY

1. MONTGOMERY, HAMILTON: Pathology of lupus erythematosus, Proc. Staff. Meet. Mayo Clin., 1940, xv, 679.
2. KIERLAND, R. R.: Classification and cutaneous manifestations of lupus erythematosus, Proc. Staff. Meet. Mayo Clin., 1940, xv, 675.
3. STOKES, JOHN H., BEERMAN, HERMAN, and INGRAHAM, NORMAN R.: The "lupus erythematosus" concept: an attempt at integration, Am. Jr. Med. Sci., 1944, ccvii, 540.
4. KLEMPERER, P., POLLACK, A. D., and BAEHR, G.: Diffuse collagen disease; acute disseminated lupus erythematosus and diffuse scleroderma, Jr. Am. Med. Assoc., 1942, cxix, 331.
5. ROSE, EDWARD, and PILLSBURY, DONALD M.: Lupus erythematosus (erythematoses) and ovarian function: observations on a possible relationship, with report of six cases Ann. Int. Med., 1944, xi, 1022.

BILATERAL SUBDURAL HEMATOMA—AN UNUSUAL COMPLICATION OF MENINGOCOCCUS MENINGITIS *

By JACK NELSON, M.D., ROBERT M. CLYNE, M.D., and J. GEORGE SHARNOFF, M.D., *New York, N. Y.*

CASE REPORT

History: C. O., a 41 year old male, was admitted to Lincoln Hospital on November 14, 1944 with a five day history of chills and fever together with "red-colored" urine. Two days subsequently he began to have generalized aches and pains. On the day of admission he became increasingly weak, fell to his knees, and was brought to the hospital.

Physical Examination: The patient appeared acutely ill but alert and oriented. The temperature was 104.4° F.; the pulse was 120. The respirations were 40 per minute, and the blood pressure was 102 mm. Hg systolic and 70 mm. diastolic. There was slight infection of the throat. The heart and lungs were clear, and the abdomen was normal. The deep tendon reflexes were equal and active throughout. There were no abnormal reflexes. The neck was flaccid, and there were no other signs of meningeal irritation.

Laboratory Examination: The urine contained 15 erythrocytes per high power field but was otherwise normal. The blood showed: hemoglobin 90 per cent (Sahli), leukocytes 16,800, polymorphonuclears 86 per cent (including 14 per cent immature forms), lymphocytes 12 per cent, monocytes 2 per cent. A roentgenogram of the chest was normal with respect both to heart and lungs. The blood urea nitrogen was

* Received for publication September 10, 1945.

From the Medical Service of Dr. Kenneth Taylor, Lincoln Hospital, New York City, N. Y.

Dr. Robert O. Kellog, Jr. participated in the clinical management of this case.

25 mg. and the blood sugar 102 mg. per 100 c.c. The blood Kline reaction was negative.

Course: On symptomatic therapy including aspirin there was temporary improvement. However, on the second hospital day the temperature rose to 102.4° F., the patient became stuporous, and the neck was suggestively rigid. A lumbar puncture revealed cloudy fluid with an initial pressure of 280 mm. of water. There were 20,000 leukocytes per cu. mm. with a large predominance of polymorphonuclear cells. The protein was 942 mg. per 100 c.c. and the sugar was less than 10 mg. per 100 c.c. Both smear and culture of the cerebrospinal fluid and culture of the blood revealed meningococcus Group I.

Sulfadiazine therapy was instituted at this time; 5 gm. were given intravenously as an initial dose, and this was followed by 1 gm. intravenously every four hours. On the third day of hospitalization the patient appeared worse, with a temperature of 103.4° F. and marked meningeal signs. The eyes were deviated to the left, and there was a fine horizontal nystagmus. There were also a right central facial paresis and a paresis of the right arm and leg. The right abdominal reflex was absent, and there was a right Babinski reflex. Lumbar puncture at this time revealed fluid which was still grossly purulent and was positive for meningococci on smear and culture.

In addition to the sulfadiazine therapy which was continued at the rate of 1 gm. every four hours, penicillin was administered at the rate of 20,000 units intrathecally once daily and 20,000 units intramuscularly every three hours. During the following two days, despite the persistence of neurologic signs and the maintenance of the temperature in the range between 101.0° and 103.5° F., the patient seemed improved with respect both to his mental state and his general condition. However, on the evening of the fifth hospital day the patient began to have generalized convulsive seizures with greater involvement of the right side. These recurred approximately every 10 to 20 minutes. Fluid obtained by lumbar puncture during this period was still cloudy but less so than previously. The initial pressure was 130 mm. of water. There were 6,650 polymorphonuclear cells per cu. mm. The protein was 540 mg. and the sugar was still less than 10 mg. per 100 cu. mm. A few meningococci were seen on smear but the culture was sterile. Despite continued therapy with sulfadiazine and penicillin the convulsions persisted for the next 30 hours until the patient died on the seventh hospital day.

Pathologic Report: Postmortem examination was performed eight hours after death. On external examination the body was that of a well developed, well nourished male. The skin was clear. The right pupil was slightly more dilated than the left.

Gross Pathology: Heart: The heart was normal in size and configuration and revealed a small triangular area of myocardial fibrosis in the lateral wall of the left ventricle. *Lungs:* Several small patches of pneumonic consolidation were noted in the mid-portion of the upper lobe of the right lung. The tracheobronchial membranes were markedly reddened. *Liver, Spleen, Pancreas and Adrenals:* These organs revealed nothing remarkable.

Kidneys: The kidneys were of normal size and configuration. Several small mucosal hemorrhages were noted in the calyces and pelves of both kidneys.

Gastrointestinal Tract: Two cm. above the pylorus on the posterior wall was a shallow, somewhat irregular ulceration of the gastric mucosa measuring 0.5 cm. in diameter. The base of the ulcer revealed a deep brown pigmentation. Immediately beyond the pyloric ring there was seen a second, deeper ulcer measuring 1.3 cm. in diameter. The edge of this ulcer was smooth and thickened. The lower half of the jejunum and the entire ileum were filled with tarry material.

Brain: When the dura mater was opened, two large, flat masses of recently clotted blood, one over each hemisphere, were found in the subdural space over the convex cerebral surfaces. The blood clot on the left was somewhat larger. The



FIG. 1.

leptomeninges were greatly thickened by a greenish-yellow, gelatinous material. Cut sections of the brain were normal.

Histopathology: Lungs: There was an exudate of polymorphonuclear cells and fibrin in the bronchioles and in a moderate number of alveoli in sections taken from the right upper lobe.

Stomach: The mucosa and muscularis mucosa were eroded in the areas of ulceration. The submucosa was markedly edematous. The blood capillaries in the base of the ulcers were greatly distended by coagulated blood. A small amount of fibrosis was seen (figure 1).

Brain: The blood vessels of the leptomeninges were markedly dilated, the tissues edematous. A moderate number of degenerating polymorphonuclear cells and lymphocytes were seen. The cytoplasm of these cells was vacuolated, and many of the nuclei were undergoing karyolysis (figure 2).



FIG. 2.

DISCUSSION

It was evident from the autopsy examination that the meningococcus meningitis had almost entirely subsided. No organisms were seen on histologic sec-

tion, and the exudate was that of a process undergoing resolution. The outstanding feature of the case at the time of death was the finding of multiple hemorrhages. There was bleeding into the subdural space and intestinal lumen and, to a lesser degree, into the mucosa of the genito-urinary tract. Death resulted from the massive subdural hemorrhages, and for this bleeding no obvious source could be determined.

That a hemorrhagic tendency is part of the syndrome of meningococcal infections has been evident since the earliest reports of this disease drew attention to the purpuric nature of the rash. However, the frequency and variety of these hemorrhages have often gone unrecognized. The first case of hemorrhage into the adrenal glands consequent upon meningococcal infection (the condition subsequently to be associated with the names of Waterhouse and Friderichsen) was reported in 1894.¹ In the years following, epistaxis, hematemesis, melena and hematuria were encountered from time to time in patients having this disease. In 1916 Denehy,² in a study of an epidemic occurring during World War I, alluded to hemorrhage into the brain and into the subarachnoid space. He also described two striking instances of multiple hemorrhages into the substance of the lung and one case of massive bleeding into the intestinal lumen. In 1922 Gordon³ reported a case of massive hemothorax resulting from meningococcal infection. And more recently Banks and McCartney⁴ have described the occurrence of extradural hemorrhage about the spinal cord at the thoracic level.

The precise pathogenesis of hemorrhage in meningococcal infection has not been determined.⁵ The histologic study of small hemorrhages⁶ reveals an involvement of the capillaries by thrombosis together with cloudy swelling of the capillary walls and exudation into the perivascular spaces. Whether this process is adequate to explain massive bleeding is not clear. An alternative explanation which has suggested itself is the minute ulceration of small blood vessels either following the lodgement of tiny meningococcal emboli within the capillaries⁷ or on the basis of devitalization within areas of purpura. Ulceration has repeatedly been seen in the skin following severe rashes.⁸ And yet often, as in the case of massive intestinal hemorrhage reported by Denehy and in the subdural hemorrhage we have encountered, no bleeding point can be found.

Hemorrhage into the subdural space as a complication of meningococcal infection is evidently rare. The only mention of it to be found in the literature occurs in a report on "Meningococcal Encephalitis" by Banks and McCartney in 1942. The case in which it was noted deserves to be described in some detail.

A 19 year old male was admitted to the hospital in coma. Thirty hours previously he had become ill and 11 hours before admission he had lapsed into stupor. Examination revealed coma with restlessness and rigidity of the neck. There was no papilledema. The right pupil did not react to light. The cerebrospinal fluid was under a pressure of 300 mm. of water. Meningococci were found on smear and culture. A course of sulfathiazole therapy was begun. On the second hospital day a right lower facial paresis appeared. On the third hospital day coma persisted, and the respiration remained stertorous. The cerebrospinal fluid was salmon-pink in color and had 12,000 cells. Meningococci were observed on smear, but culture proved sterile. During this day there was moderate improvement; the patient became oriented and "spoke a few words." On the fourth and fifth hospital days, however, there was a relapse into deep coma, breathing became stertorous again, and the pupils appeared dilated and fixed. The cerebrospinal fluid was again salmon-pink in color

and under high pressure. The cells had decreased to 5,300 and, although meningococci were found on smear, culture again proved sterile. During the following day there appeared convulsions, hyperthermia (temperature 107° F.) and death.

Autopsy revealed a subdural hematoma two inches long over the left temporal lobe. There was a very scanty purulent exudate over the base of the brain and within the ventricles. The brain and spinal cord were congested and edematous, and a small hemorrhage was found in the mid-brain.

It will be observed that the case we are reporting and the one just summarized bear a marked similarity with respect to certain clinical features. The syndrome of meningitis was predominant during the early course of both cases. Furthermore, in both instances there was transient clearing of the mental state together with suggestive evidence that the meningitis was beginning to come under control (falling leukocyte count and sterile culture). And following this, both patients returned to coma with an increase of general and focal neurologic signs leading to death.

It should be pointed out that this pattern of events is in contrast to the expected course of meningococcus meningitis. It has been our experience that the meningitis of itself almost invariably responds promptly to adequate sulfonamide therapy and that, having responded, it does not relapse.⁹ On the other hand, hemorrhagic encephalitis, when it occurs as a complication of meningococcal infection, comes at the onset and is rapidly fatal. It is obvious that the clinical differentiation of subdural hematoma from the context of meningitis or from the complication of hemorrhagic encephalitis presents considerable difficulty. Yet the timely employment of neurosurgery is so effective in the treatment of such hematoma that the diagnosis of this condition may be life saving.

BIBLIOGRAPHY

1. VOELKER, A. F.: Item in Path. Reports Middlesex Hospital, 1894, p. 246.
2. DENEHY, W. J.: Epidemic cerebrospinal meningitis, Brit. Med. Jr., 1916, ii, 684.
3. GORDON: 1922 (Quoted from Briton—reference below).
4. BANKS, H. S., and McCARTNEY, J. E.: Meningococcal encephalitis, Lancet, 1942, i, 219.
5. BRITON, D.: Cerebrospinal fever, 1941, London, 152 pp.
6. (a) NETTER, A., and DEBRÉ, R.: La méningite cérébrospinale, 1911, Paris.
(b) BANKS, H. S., and McCARTNEY, J. E.: Meningococcal adrenal syndromes and lesions, Lancet, 1943, i, 711.
(c) Reference 4, above.
7. MURRAY, E. G. D.: The Meningococcus Medical Research Council Special Report Series, No. 124, H. M. Stationery Office, London, 1929.
8. WORSTER-DROUGHT, C., and KENNEDY, A. M.: Cerebrospinal fever, 1919, A. and C. Black, London.
9. APPELBAUM, E., and NELSON, J.: Sulfadiazine and its sodium compound in the treatment of meningococcic meningitis and meningococcemia, Am. Jr. Med. Sci., 1944, ccvii, 492.

EDITORIAL

THE CONCEPT OF HYPERSPLENISM

THE intimate relationship of the spleen to hematopoiesis has been recognized for many years. This correlation has been exemplified in the past by the catch-all term *splenic anemia* formerly widely used to describe almost any syndrome characterized by splenomegaly and anemia. However, in contradistinction to the many recent advances in knowledge of the normal and pathological physiology of other organs and systems, information concerning the activities of the spleen has been relatively scanty. Such information as has accumulated has often been deduced from observations made in pathological states. The concept of hypersplenism is typical of this approach.

In 1916 Kaznelson¹ demonstrated that the removal of the spleen resulted in a prompt rise in the peripheral platelet count and consequent clinical improvement of some cases of thrombocytopenic purpura. It was postulated that the spleen exerted an excessive cytolytic effect upon platelets. However, following the widespread use of bone marrow study in such cases in recent years megakaryocytic hyperplasia has been regularly observed in essential thrombocytopenic purpura. Two schools of thought exist as to the pathogenetic mechanism: (1) that the hyperplasia is a compensatory phenomenon resulting from excessive phagocytosis of circulating platelets, or (2) that it represents maturation arrest due to excessive inhibition by an overactive spleen. Recent studies by Dameshek and Miller² demonstrate not only quantitative alterations in megakaryocytes but well-defined qualitative changes characterized chiefly by lack of platelet formation from the cytoplasm of these cells. Since removal of the spleen results in prompt and dramatic change in the megakaryocytes with the outpouring of platelets into the peripheral blood it is suggested that recovery is essentially due to the removal of an overactive splenic humoral, possibly hormonal, substance, i.e., splenectomy results in the correction of a state called with some propriety, hypersplenism.

That an intimate relationship exists between the spleen and the level of granulocytes in the peripheral blood is evidenced by the effect of removal of the normal spleen in the experimental animal and in man. Extirpation of the spleen results in a prompt and often quite marked granulocytic leukocytosis which may persist for some time. Frank³ in 1916 first described an entity which he named *aleukia splenica* and which apparently escaped

¹ KAZNELSON, P.: Verschwinden der hämorrhagischen Diathese bei einem Falle von "essentieller Thrombopenie" (Frank) nach Milzexstirpation. Splenogene thrombolytische Purpura, Wien. klin. Wchnschr., 1916, xxvi, 1451-1454.

² DAMESHEK, W., and MILLER, E. B.: The megakaryocytes in idiopathic thrombocytopenic purpura, a form of hypersplenism, Blood, 1946, i, 27-51.

³ FRANK, E.: Aleukia splenica, Berl. klin. Wchnschr., 1916, liii, 555.

widespread clinical recognition until recently when Doan and Wiseman⁴ clearly delineated the clinical and hematological features of a syndrome called by them *primary splenic neutropenia*. The syndrome is characterized by marked leukopenia, splenomegaly and a normal or even hyperplastic marrow. The existence of neutropenia predisposes to recurring episodes of pyogenic infection. Acute, subacute and chronic varieties have been described. Splenectomy, performed after careful studies have ruled out other pathological states, results in prompt rise in the leukocyte count and clinical improvement of the patient. The effect is fully as dramatic as that observed in essential thrombocytopenic purpura. To date approximately twelve such cases have been recorded in the literature by a number of observers.

No information exists yet as to the initiating causes. Doan and Wiseman describe excessive phagocytosis of leukocytes by reticulo-endothelial cells of the pulp studied by a supravital staining technic. Routine histopathological studies of the spleen usually fail to demonstrate significant changes. A humoral or hormonal mechanism is again postulated and the syndrome is regarded as an example of hypersplenism in which the inhibitory effect is directed almost entirely against the neutrophilic leukocytes.

In some of the recorded cases of splenic neutropenia associated moderate reduction in the erythrocyte and platelet counts has been observed. A logical extension of the concept of hypersplenism would be a syndrome characterized by depression of all cellular elements derived from the bone marrow. Such an entity has recently been described by Doan and Wright⁵ and is referred to as *primary splenic panhematopenia*. Two cases are reported, one an apparently congenital variety, the other an acute form. The clinical importance of the recognition of this entity lies in its separation from the general group of inevitably fatal aplastic anemias. Although *primary splenic panhematopenia* probably constitutes but a small fraction of such cases, the vastly improved prognosis after splenectomy renders their separation imperative.

It is obvious from consideration of the accumulated data, that the spleen has more than a passive function as a reservoir of red blood cells or even as the "graveyard" of erythrocytes. Evidence indicating a possible endocrine function is still scanty. Such a possibility has been postulated for a number of years but no valid proof existed. Within recent years a few bits of data have accumulated. Thus in 1938 Troland and Lee⁶ reported the isolation of a substance from acetone extracts of spleens removed for essential thrombocytopenic purpura which induced temporary reduction of the platelet count after injection into animals. The existence of "Thrombocytopen,"

⁴ WISEMAN, B. K., and DOAN, C. A.: Primary splenic neutropenia; a newly recognized syndrome, closely related to congenital hemolytic icterus and essential thrombocytopenic purpura, *Ann. Int. Med.*, 1942, xvi, 1097-1117.

⁵ DOAN, C. A., and WRIGHT, C. S.: Primary congenital and secondary acquired splenic panhematopenia, *Blood*, 1946, i, 10-26.

⁶ TROLAND, C. E., and LEE, F. C.: Thrombocytopen. A substance in the extract from the spleen of patients with idiopathic thrombocytopenic purpura that reduces the number of blood platelets, *Jr. Am. Med. Assoc.*, 1938, cxi, 221-226.

as it was named, has been a moot question. Its status is still disputed at this time. Dameshek² has reported recently that saline extracts of similar spleens produced profound thrombocytopenia with characteristic bone marrow changes in dogs. Evidence of another sort has recently been contributed by Ungar.⁷ He reports the isolation of a crystalline substance from guinea pig spleen which he terms "Splenin." This substance reduces the bleeding time, and increases capillary resistance in the experimental animal. Its secretion into the blood is believed to be part of the pituitary-adrenal response to stress. Splenectomized animals injected with cortico-trophic hormone or adrenal cortical extract do not display the characteristic drop in bleeding time observed in normal animals. Ungar believes that these studies demonstrate clearly an endocrine function of the spleen. What relation, if any, exists between "Thrombocytopen" and "Splenin" is not clear at this time.

If the concept of hypersplenism is further supported by experimental data one might be justified in postulating a eusplenic and even a hyposplenic state. At this time it would be obviously impossible to do more than speculate upon the probable clinico-pathological manifestations of the latter condition.

M. S. S.

⁷ UNGAR, G.: Endocrine function of the spleen and its participation in the pituitary-adrenal response to stress, *Endocrinology*, 1945, xxxvii, 329-340.

REVIEWS

Topley and Wilson's *Principles of Bacteriology and Immunity*. By G. S. WILSON, M.D., F.R.C.P., D.P.H., K.H.P., and A. A. MILES, M.A., F.R.C.P. Third Edition. Two Volumes. 2054 pages; 16.5 × 23.5 cm. Williams and Wilkins Co., Baltimore. 1946. Price, \$12.00.

This new revision of an important and comprehensive work will be welcomed by bacteriologists and others interested in infectious diseases. The general plan of presentation of the second edition has been retained. The text has, as formerly, been divided into two volumes with the index conveniently appended to both.

Volume I contains the sections on General and Systematic Bacteriology. Under General Bacteriology are discussed characteristics of bacteria, principles of disinfection, antigenic structure, the antigen-antibody reaction and bacteriophage. There is a new chapter on antibacterial substances used in the therapy of infections. Part II, after some introductory material on methods, consists of discussions by genera of the various organisms encountered in medical bacteriology. The nomenclature employed is a modified version of the American system, especially of the form set forth in the report of the committee of the Society of American Bacteriologists in 1920. A notable innovation is the recognition of the terms *Salmonella* and *Shigella* for designation of organisms previously included in the *Genus Bacterium*.

In the second volume are the sections: Infection and Resistance and The Application of Bacteriology to Medicine and Hygiene. In the latter, which is chiefly a series of chapters on specific infections, the number of virus diseases included has been greatly increased and the lymphogranuloma-psittacosis group is taken up separately. The book closes with considerations of the bacteriology of man, air, milk, and water, shellfish and sewage. The new chapter on aerobiology reviews recent developments in the disinfection of air in closed spaces. A discussion of soil bacteriology and natural economy has unfortunately been deleted.

With the exceptions noted, the changes have been minor ones—mainly the insertion of new material—so that, as a result, the edition is longer than that of 1936. The preface contains an apology for not having been more concise and some readers will agree that part of the detail might have been profitably omitted. The treatment of different subjects with respect to recent knowledge is perhaps unavoidably a little uneven. However, on the whole, the book retains its high standard of excellence and will undoubtedly be widely used both as a text and for reference work. The wealth of information and the extensive bibliographies provide a sound basis for entry into almost any line of investigation in medical bacteriology.

H. D. V.

Neurosyphilis. By H. HOUSTON MERRITT, A.B., M.A., M.D., Professor of Clinical Neurology, College of Physicians and Surgeons, Columbia University; RAYMOND D. ADAMS, M.A., M.D., Associate in Neurology, Harvard Medical School; and HARRY C. SOLOMAN, B.S., M.D., Professor of Psychiatry, Harvard Medical School. 443 pages; 24 × 16 cm. Oxford University Press, New York. 1946.

The authors adequately state the purpose of the text in their preface as follows: "... a text book which approached these problems from the point of view of the neurologist and the psychiatrist and at the same time critically appraised modern treatment methods." They have followed their original purpose and the final result is an excellent modern treatise on neurosyphilis. The bibliography at the end of each chapter is adequate. There are chapters dealing with fever therapy, tryparsamide, and penicillin. They have approached the individual problems by presenting the in-

dications, contraindications, advantages, and disadvantages of all methods of diagnosis and treatment. An interesting feature is the presentation of case reports throughout the text. This is a book which, in the opinion of this reviewer, should occupy a space in the library of the general practitioner and specialist.

H. M. R.

Gastro-enterology. By HENRY L. BOCKUS. Volume I. 831 pages; 25.5 × 17 cm. W. B. Saunders Company, Philadelphia. 1943. Price, \$12.00.

Dr. Bockus has written a three volume work on gastro-enterology which has been hailed as a monumental contribution. The first volume which is here reviewed deals with the esophagus and stomach; Volume II with the small and large intestines and peritoneum; Volume III with the liver, biliary tract and pancreas.

The first section of Volume I deals with the examination of the patient and includes history taking, symptomatology, physical examination and laboratory examinations in gastrointestinal diseases.

Section II includes disorders of the esophagus and diaphragm with an excellent discussion of the anatomy and physiology of these structures, which introduces the pathological entities such as hiatus hernia, esophageal stricture, cardiospasm, etc. The coincidence of cardiospasm and pneumonia is properly emphasized.

Diseases of the stomach are discussed in Section III and again, a summary of the fundamental anatomy and physiology precedes the consideration of the various morbid states.

The excellent format of this book facilitates its perusal. Illustrations in the form of roentgenograms, drawings and photographs are reproduced with unusual clarity. The listings in the index are complete and orderly, increasing greatly the value of the book for reference purposes.

Dr. Bockus has successfully incorporated his own vast experience in these pages. The completed work, as judged by the quality of this first volume, will be an important addition to the literature on gastro-enterology.

J. Z. B.

BOOKS RECEIVED

Books received during September are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

X-Rays and Radium in the Treatment of Diseases of the Skin. Fourth Edition, Revised. By GEORGE M. MACKEE, M.D., and ANTHONY C. CIPOLIARO, M.D. 668 pages; 24 × 15.5 cm. 1946. Lea & Febiger, Philadelphia. Price, \$10.00.

Renal Hypertension. By EDUARDO BRAUN-MENENDEZ, JUAN CARLOS FASCILOLO, LUIS F. LELOIR, JUAN M. MUNOZ, and ALBERTO C. TAQUINI, Buenos Aires. Translated by LEWIS DEXTER, M.D. 451 pages; 23.5 × 16 cm. 1946. Charles C. Thomas, Springfield, Ill. Price, \$6.75.

Principles of Hematology. Third Edition, Revised. By RUSSELL L. HADEN, M.A., M.D. 366 pages; 24 × 15.5 cm. 1946. Lea & Febiger, Philadelphia. Price, \$5.00.

Early Ambulation. By DANIEL J. LEITHAUSER, M.D., F.A.C.S. 232 pages; 23.5 × 16 cm. 1946. Charles C. Thomas, Springfield, Ill. Price, \$4.50.

Dentistry: An Agency of Health Service. By MALCOLM WALLACE CARR, D.D.S. 219 pages; 21.5 × 14 cm. 1946. The Commonwealth Fund, New York. Price, \$1.50.

- Treatment of Bronchial Asthma.* By VINCENT J. DERBES, M.D., and HUGO TRISTRAM ENGELHARDT, M.D., F.A.C.P. 466 pages; 24 × 16 cm. 1946. J. B. Lippincott Company, Philadelphia. Price, \$8.00.
- Penicillin; Its Practical Application.* By multiple authors under the Editorship of Professor SIR ALEXANDER FLEMING, M.B., B.S., F.R.C.P., F.A.S. 380 pages; 22.5 × 14.5 cm. 1946. The Blakiston Company, Philadelphia. Price, \$7.00.
- The Drama of Sex.* By JAMES LINCOLN MCCARTNEY, M.D., F.A.C.P. 147 pages; 22 × 14.5 cm. 1946. Stratford House, Inc., New York. Price, \$2.50.
- If You Ask My Advice.* By HENRY PLEASANTS, JR., M.D. 110 pages; 21 × 14 cm. 1946. Bruce Humphries, Inc., Boston. Price, \$2.00.
- Environmental Warmth and Its Measurement.* With 10 charts. By T. BEDFORD, D.Sc. 40 pages. British Information Services, New York. 1946.
- Psychotherapy in General Practice.* Report of an experimental postgraduate course. By GEDDES SMITH. 38 pages. The Commonwealth Fund. 1946. Price, .25.

COLLEGE NEWS NOTES

REDUCTION IN THE SIZE OF THE SECTION ON COLLEGE NEWS NOTES

Owing to the critical shortage of paper it will be necessary for an indeterminate period to limit the publication of College News Notes. This decision, taken at the recent meeting of the Board of Regents, has been given partial effect in the present issue, but will apply more drastically to ensuing numbers until an adequate supply of paper is once more available.

In the reduced space priority will be given to the announcements of future meetings, conferences or assemblies of special interest to internists, and to important awards to College members.

Dr. David P. Barr, F.A.C.P., President, officially represented the American College of Physicians at the meeting of the American Diabetes Association in Toronto, during September, which marked the 25th anniversary of the discovery of insulin.

The Forty-third Annual Congress on Medical Education and Licensure will meet February 10 and 11, 1947, at the Palmer House, Chicago.

DR. F. M. POTTENGER AGAIN HONORED

Dr. Frank M. Pottenger, F.A.C.P., Monrovia, Calif., former President and for many years a Regent of the American College of Physicians, was tendered a great birthday party by more than three hundred friends and former patients at the Pottenger Sanatorium and Clinic, on September 22, although his 77th birthday did not occur until September 27. Former patients came from far and near to pay tribute. Dr. Pottenger founded the Sanatorium in 1903, and during the interim more than 6,000 patients have been treated there.

The appointment of Dr. Howard A. Rusk, F.A.C.P., New York, to head the new Department of Rehabilitation and Physical Medicine of the New York University College of Medicine, has been announced. In addition to instructing medical students in problems and technics in this field, the department will cooperate with hospital authorities of New York City in establishing and supervising programs for the rehabilitation of patients in all of the city hospitals.

Dr. Rusk established the rehabilitation program of the Army Air Forces in 1942; upon this program were patterned those of the Army Service Forces, the Navy, the U. S. Public Health Service and the Veterans Administration. Dr. Rusk will continue his activities as Associate Editor of the New York Times, and consultant to the Medical Director of the Veterans Administration.

Rear Admiral John Harper, (MC), USN, F.A.C.P., Washington, D. C., has been awarded the Legion of Merit, "for exceptionally meritorious conduct in the performance of outstanding services in the planning, development and establishment of the United States Naval Hospital, National Naval Medical Center, Bethesda, Md., from the outbreak of hostilities until Feb. 4, 1942, and as medical officer in command of this hospital from Feb. 5, 1942 to April 12, 1945."

Dr. Paul R. Hawley, F.A.C.P., Chief Medical Director of the Veterans Administration, recently announced the appointment of Dr. Samuel M. Bittinger, F.A.C.P.,

Sanatorium, N. C., as Chief of Section, Tuberculosis Unit, VA Hospital, Oteen, N. C.; Dr. George C. Wilson, F.A.C.P., Wallingford, Conn., as Assistant Chief, Tuberculosis Section, VA-Branch Office No. 1, Boston; Dr. Morris C. Thomas (Associate), Indianapolis, as Chief of Section, Tuberculosis Unit, VA Hospital, Dayton, Ohio.

The appointments of 18 Fellows and two Associates of the College to be civilian consultants to the Secretary of War, through the Surgeon General, were recently announced. These were as follows:

Internal medicine: Dr. Arthur C. Curtis, F.A.C.P., Ann Arbor, Mich.; Dr. Francis R. Dieuaide, F.A.C.P., New York; Dr. Garfield G. Duncan, F.A.C.P., Philadelphia; Dr. Edgar Durbin, F.A.C.P., Denver; Dr. Lester C. Feener (Associate), El Paso, Tex.; Dr. Harry T. Harper, Jr., F.A.C.P., Augusta, Ga.; Dr. William J. Kerr, F.A.C.P., San Francisco; Dr. Orlando B. Mayer, F.A.C.P., Columbia, S. C.; Dr. John B. McKee, F.A.C.P., Winchester, Va.; Dr. William S. Middleton, F.A.C.P., Madison, Wis.; Drs. Samuel Morrison, F.A.C.P., and Maurice C. Pincoffs, F.A.C.P., Baltimore; Dr. Monroe J. Romansky (Associate), Silver Spring, Md.; Dr. S. Marion Salley, F.A.C.P., Miami, Fla.; Dr. James J. Waring, F.A.C.P., Denver; Dr. Wallace M. Yater, F.A.C.P., Washington, D. C.

Neuropsychiatry: Dr. Hervey M. Cleckley, F.A.C.P., Augusta, Ga.; Dr. Walter Freeman, F.A.C.P., Washington, D. C.

X-Ray: Dr. Arthur C. Christie, F.A.C.P., Washington, D. C.

Radiology: Dr. Edgar M. McPeak, F.A.C.P., Washington, D. C.

At its meeting in New York the first week in September, the American Congress of Physical Medicine awarded Dr. Ralph Pemberton, F.A.C.P., Philadelphia, the Distinguished Service Gold Key for outstanding accomplishments in the field.

Colonel James E. Ash, (MC), USA, F.A.C.P., Washington, D. C., Director of the Army Institute of Pathology, received the following tribute from the American Society of Clinical Pathologists: "The Army Institute of Pathology has contributed immeasurably to the increasing knowledge in the medical field, particularly that of pathology, and has reflected credit on the Army Medical Department and the United States Army, and has fostered a military-civilian liaison that was nothing short of priceless in World War II. The leadership for these far reaching projects was from 1937 to the present vested in Colonel James E. Ash from whose inspiration, judgment and scientific acumen stemmed the success of many of these projects."

Dr. Howard F. West, F.A.C.P., Los Angeles, President of the American Heart Association, Inc., has designated February 9-15, 1947, as National Heart Week. During this week the educational activities of the Association, which emphasize the importance of rheumatic fever and heart disease in children, will reach a climax. The American College of Physicians is supporting and coöperating in the work of the American Council on Rheumatic Fever of the Association.

The National Gastroenterological Association at its Annual Convention Banquet, June 1947, will award \$100 and a certificate of merit for the best unpublished contribution on gastroenterology or allied subjects in its 1947 Award Contest. Additional certificates will be awarded to worthy, but less meritorious, contributions. Contestants must be members of the American Medical Association or similar organizations in other countries. The Association reserves exclusive right to publish the honored con-

tributions in The Review of Gastroenterology. Entries should be limited to 5,000 words, typewritten in English in manuscript form, and submitted not later than April 1, 1947, accompanied by an entry letter, to the Association, 1819 Broadway, New York 23, N. Y.

The appointment of Dr. John B. Youmans, F.A.C.P., Nashville, Tenn., to the Deanship of the University of Illinois College of Medicine was recently announced. Dr. Youmans is presently Professor of Medicine and Acting Dean of the Vanderbilt University School of Medicine. He graduated in 1919 from the Johns Hopkins University School of Medicine, became a Fellow of the College in 1925, and is a diplomate of the American Board of Internal Medicine. Dr. Youmans served during 1940-41 as a member of the Rockefeller Foundation Health Commission to Europe. He is a Fellow of the American Medical Association, and a member of the Southern Medical Association, American Society for Clinical Investigation, American Clinical and Climatological Association, and of the Association of American Physicians.

Dr. Harold Swanberg, F.A.C.P., Quincy, Ill., recently received the Distinguished Service Award for 1946 of the Mississippi Valley Medical Society, "in recognition of unusual and distinguished services as editor, as administrator and as founder of medical periodicals and societies, of a medical library and of endowment funds and a foundation, all of them designed to help physicians in private practice to continue their education; to stimulate clinical research; to promote good fellowship and advance the interests of the members of the profession; and to make more readily available, especially in rural and urban areas, a higher quality of medical service; and in appreciation of his zealous and untiring efforts in behalf of the Society and its members."

The series of Friday Afternoon Lectures of the New York Academy of Medicine, 1946-47, will include the following by Fellows of the College:

December 6, Dr. Z. Taylor Bercovitz, New York, "Colitis."

January 3, Dr. A. J. Carlson, Chicago, "The Treatment of Chronic Alcoholism by the General Practitioner."

March 28, Dr. Lloyd F. Craver, New York, "Recent Advances in the Treatment of Lymphomas and Leukemias."

Dr. Francis J. Braceland, F.A.C.P., has retired from active duty in the U. S. Naval Reserve, where he had the rank of Captain, and is now Consulting Psychiatrist to the Mayo Clinic and Professor of Psychiatry, Mayo Foundation, University of Minnesota Graduate School.

Dr. John Q. Griffith, Jr., F.A.C.P., Philadelphia, Pa., Dr. M. August Lindauer (Associate), Philadelphia, Pa., Dr. Ralph L. Shanno, F.A.C.P., Forty Fort, Pa., and Dr. James F. Couch, Eastern Research Laboratory of the U. S. Department of Agriculture, were awarded a Certificate of Merit by the American Medical Association at the San Francisco meeting for an exhibit entitled "Rutin: Treatment for Hypertension Associated with Increased Capillary Fragility."

Dr. Ralph L. Shanno, F.A.C.P., Forty Fort, Pa., Dr. John Q. Griffith, Jr., F.A.C.P., Philadelphia, Pa., and Dr. William LaMotte, Jr., Philadelphia, Pa., received an award for a scientific exhibit at the Philadelphia meeting of the Medical Society of the State of Pennsylvania, held during October, 1946, for an exhibit entitled "Capillary Fragility and Capillary Permeability in Relation to Retinal Hemorrhage."

EMORY UNIVERSITY OFFERS INFORMAL COURSES OF POSTGRADUATE TYPE

Dr. Russell H. Oppenheimer, F.A.C.P., Professor of Clinical Medicine at Emory University, Atlanta, Ga., has recently announced that the University will offer informal courses of instruction of a postgraduate type to men in practice. These are arranged for varying periods of time, preferably for a three months or quarter basis. They will, however, take students for periods as short as two weeks.

At the Fortieth Annual Meeting of the Southern Medical Association, which occurred November 4-7, at Miami, Fla., Dr. William H. Sebrell, Jr., F.A.C.P., Bethesda, Md., was presented with the Association's Research Medal for his studies on nutrition in relation to public health.

The Canadian Medical Procurement and Assignment Board published a very valuable guide for medical officers retiring from active duty. The pamphlet is entitled, "Facts about Your Medical Career on Demobilization." The publication gives detailed information concerning the advantages and opportunities to which retiring medical officers are eligible. It reviews in some detail the matter of refresher courses, postgraduate training, placement, and miscellaneous appointments. It contains a complete survey of medical refresher courses, internships, residencies, assistantships, fellowships, etc.

Copies are available through the Canadian Medical Association, 184 College St., Toronto, or through the headquarters of the Board at Ottawa.

Dr. Abraham M. Kleinman (Associate), Brooklyn, N. Y., has been awarded the Army Commendation Ribbon in recognition of his services as Assistant Chief and Chief of Medical Service at Halloran General Hospital, Staten Island, N. Y.

AMERICAN COLLEGE OF PHYSICIANS REGIONAL MEETINGS

NORTH CAROLINA

Under the Governorship of Dr. Paul F. Whitaker, F.A.C.P., Kinston, a Regional Meeting of the College for North Carolina took place October 18, at Winston-Salem. The scientific program was as follows: The Diagnosis and Treatment of Rheumatoid Spondylitis, Dr. Richard Z. Query, Jr., F.A.C.P., Charlotte, N. C.; The Technic and Value of Therapeutic Pneumoperitoneum, Dr. Joseph S. Hiatt, Jr. (Associate), Sana-torium, N. C.; Cecal Granulomata, Dr. Charles M. Caravati, F.A.C.P., Richmond, Va.; Surgery of Patent Ductus Arteriosus (Moving pictures), Dr. Howard H. Bradshaw, Winston-Salem, N. C.; Clinico-Pathological Conference, Drs. Oscar E. Hansen-Pruss, Durham, N. C. and Robert P. Morehead, F.A.C.P., Winston-Salem, N. C.

An informal dinner at the Old Town Club followed the scientific sessions. The guest address was delivered by Dr. Leslie B. Hohman, Visiting Professor of Psychiatry, Duke University. Dr. Whitaker also spoke at the dinner.

NORTH CENTRAL STATES

A Regional Meeting of the College for the states of Illinois, Indiana, Iowa, Kentucky, Michigan, Minnesota and Wisconsin, occurred at Chicago, November 16. Dr. Walter L. Palmer, Governor for Northern Illinois, served as Chairman of the Local Program Committee. Drs. Douglas Donald, Cecil M. Jack, Robert M. Moore, Karver L. Puestow, and B. F. Wolverton, Governors for Michigan, Southern Illinois, Indiana, Wisconsin, and Iowa, respectively, presided at the meetings. Dr. Andrew C.

Ivy, F.A.C.P., Vice President and Distinguished Professor of Physiology, University of Illinois, spoke at the evening session on the topic, "War Crimes of a Medical Nature." Dr. David P. Barr, President, Dr. Chauncey W. Dowden, Chairman of the Board of Governors, Dr. Morris Fishbein, Editor of the Journal of the American Medical Association, Dr. Ernest E. Irons, Past President and Regent, Mr. Edward R. Loveland, Executive Secretary, and Dr. LeRoy Sloan, Regent and General Chairman of the 1947 Annual Convention, also addressed remarks following the dinner at which Dr. E. V. Allen, Governor for Minnesota, was Toastmaster. The scientific program was as follows: Peritoneoscopy: Clinical and Pathological Correlations in Epidemic Hepatitis, Dr. Thomas N. Horan, F.A.C.P., Detroit; Early Diagnosis and Treatment of Subclinical Liver Impairment, Dr. John G. Mateer, F.A.C.P., Detroit; Homologous Serum Jaundice, Dr. Richard B. Capps, F.A.C.P., Chicago; Amebic Hepatitis, Dr. George W. Pedigo, F.A.C.P., Louisville; Antibody Relationships of Blood Plasma Protein, Dr. Harold Duetsch, Madison; Amino Acids in Nephrosis, Dr. Douglas A. MacFagden, Chicago; The Role of Amino Acids in Nutrition, Dr. W. C. Rose, Urbana, Ill.; The Metabolism of Chiniofon, Drs. Edgar S. Gordon, F.A.C.P., and E. C. Albright, Madison, Wis.; Transport and Excretion of Uric Acid In Normal and Gouty Individuals, Drs. R. Levine and William Q. Wolfson, Chicago; The Use of Diet in the Management of Calcium Phosphate Urolithiasis, Dr. R. H. Flocks, F.A.C.S., Iowa City; Extra Renal Uremia, Dr. Francis D. Murphy, F.A.C.P., Milwaukee; Thiouracil in the Treatment of Hyperthyroidism, Dr. J. O. Ritchey, F.A.C.P., Indianapolis; End Results of Treatment of Pituitary Dwarfism with Sex Hormones, Dr. Willard O. Thompson, F.A.C.P., Chicago; Chemotherapy and Radioactive Substances in the Treatment of Diseases of the Hemopoietic System, Dr. Leon O. Jacobson, Chicago; Surgical Treatment of Hypertension, Dr. Adrien Verbrugghen, F.A.C.S., Chicago; Pulmonary Adenomatosis, Dr. Frederick J. Pohle, Madison; Neurologic Causes of Pain in the Upper Extremities, Dr. Lee M. Eaton, Rochester, Minn.; Management of Patients with Cardiospasm, Dr. Frank R. Peterson, F.A.C.S., Iowa City; Clinical Manifestations of Alkalosis, Dr. David P. Barr, F.A.C.P., New York; Vascular Emergencies, Dr. E. A. Hines, Jr., F.A.C.P., Rochester, Minn.; Present Status of Folic Acid in the Treatment of Macrocytic Anemia, Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor; Isolated Myocarditis, Dr. O. Saphir, Chicago; Disseminated Inflammatory Lesions Following Sulfonamide Administration, Dr. Eleanor M. Humphreys, Chicago; Present Status of Treatment of Bacterial Endocarditis With Penicillin, Dr. C. Phillip Miller, F.A.C.P., Chicago; Penicillin Therapy of Syphilis, Dr. J. Murray Kinsman, Louisville; Clinical Use of Streptomycin, Dr. Wallace E. Herrell, F.A.C.P., Rochester, Minn.; Present Status of the Scarlet Fever Problem, Dr. Paul S. Rhoads, F.A.C.P., Chicago; Clinical Intoxication with Potassium, Dr. Norman M. Keith, Rochester, Minn.; Cor Pulmonale: A Comparison of the Acute and Chronic Forms, Dr. Norbert Enzer, F.A.C.P., Milwaukee.

FLORIDA

Preceding the meetings of the Southern Medical Association, a Regional Meeting of the College occurred at Miami Beach, Fla., November 3 and 4, through the cooperation of Dr. Turner Z. Cason, F.A.C.P., Jacksonville, Dr. Glenville Giddings, F.A.C.P., Atlanta, Dr. E. Dice Lineberry, F.A.C.P., Birmingham, and Dr. Kenneth M. Lynch, F.A.C.P., Charleston, College Governors for Florida, Georgia, Alabama and South Carolina, respectively. Dr. Edward L. Bortz, F.A.C.P., Philadelphia, Vice-Chairman of the Board of Governors and Chairman of the Advisory Committee on Postgraduate Courses, and the visiting Governors were guest speakers at the Luncheon Meeting at the McAllister Hotel, November 4. The scientific program consisted of the following: Chronic Cor Pulmonale: Case Due to Pulmonary Artery Compression by Aneurysm of Aorta, Dr. Julius R. Pearson, F.A.C.P., Miami Beach; Climate and

Heart Disease, Dr. Herbert Eichert (Associate), Miami; Delayed Convalescence in Infectious Hepatitis, Dr. Donald F. Marion, F.A.C.P., Miami; Value and Limitations of X-ray Study of the Gastrointestinal Tract, Dr. Frederick K. Herpel, F.A.C.P., West Palm Beach; Clinic: Treatment of Cirrhosis of Liver, Dr. Franz Stewart, F.A.C.P., Miami; Clinic: Demonstration of Cardiac Cases, Drs. Charles F. Roche, F.A.C.P., and Donald F. Stannus (Associate), Miami Beach.

WESTERN MICHIGAN REGIONAL MEETING OF THE COLLEGE, GRAND RAPIDS

A Regional Meeting of the members of the American College of Physicians was held at Grand Rapids, October 30, 1946, under the chairmanship of Dr. Burton R. Corbus, F.A.C.P. The program was as follows: Bacterial Endocarditis, Dr. J. D. Venema—Discussant, Dr. L. Paul Ralph (Associate); A Group of Interesting and Unusual Arthritides, Dr. Carl B. Beeman, F.A.C.P., Grand Rapids—Discussant, Dr. William D. Robinson, F.A.C.P., Ann Arbor; Echinococcus Disease of the Lungs, Dr. Noyes L. Avery, Jr. (Associate), Ann Arbor—Surgical discussant, Dr. J. Duane Miller, F.A.C.S., Grand Rapids; Undulant Fever, Dr. Gordon W. Balyeat, F.A.C.P., Grand Rapids; Cutaneous Lymphosarcoma, Dr. Ralph L. Fitts, F.A.C.P., Grand Rapids; Social Hour; Dinner.

Guest Speaker at the dinner given at the University Club was Dr. D. Robinson. His topic was "Some Observations on Malnutrition as It Actually Occurs in Population Groups."

CORRECTIONS

In College News Notes, September 1946, page 550, the service designation USN and the address, Philadelphia, were ascribed to Dr. George Cupp Griffith, F.A.C.P. Dr. Griffith served in the Medical Corps of the Naval Reserve, and is located in Los Angeles.

In the College News Notes, August, 1946, page 389, it was incorrectly stated that "Dr. Joseph S. Hiatt, F.A.C.P., Sanatorium, N. C., has been appointed to the position of Superintendent of the Hugh Chatham Memorial Hospital, Elkin, N. C." Dr. Joseph S. Hiatt, Jr. (Associate), has in fact been appointed to the position of Associate Superintendent and Associate Medical Director of the North Carolina Sanatorium for the Treatment of Tuberculosis, Sanatorium, N. C.; Dr. Hiatt's father, the Reverend J. D. Hiatt, D. D., has been appointed Superintendent of the Hugh Chatham Memorial Hospital.

GIFTS TO THE COLLEGE LIBRARY

Dr. Ralph Bowen, F.A.C.P., Houston, Tex.—3 reprints
 Dr. Charles H. Lutterloh, F.A.C.P., Hot Springs National Park, Ark.—1 reprint
 Dr. Fred M. Meixner, F.A.C.P., Peoria, Ill.—5 reprints
 Dr. Bradford Murphey, F.A.C.P., Denver, Col.—1 reprint
 Dr. D. E. Nolan (Associate), Dayton, Ohio—3 reprints
 Dr. Aaron E. Parsonnet, F.A.C.P., Newark, N. J.—1 reprint
 Dr. Joseph T. Roberts (Associate), Washington, D. C.—1 reprint
 Dr. Carl F. Shaffer (Associate), Houston, Tex.—6 reprints
 Dr. Edward J. Stieglitz, F.A.C.P., Washington, D. C.—6 reprints
 Dr. John Mumford Swan, F.A.C.P., Rochester, N. Y.—4 reprints
 Dr. Charles C. Verstandig (Associate), New Haven, Conn.—1 reprint
 Dr. R. Lomax Wells, F.A.C.P., Washington, D. C.—1 reprint

The College acknowledges with thanks to the author, Dr. Edward R. Janjigian (Associate), Edinburg, Ind., a copy of his novel, entitled "Doctor Destiny," which has been added to the College Library.

RETIREMENTS FROM SERVICE

Since the last publication of this journal, the following members of the College have been reported retired or on terminal leave (to October 12, 1946 inclusive).

Frank M. Adams, Hot Springs National Park, Ark. (Lt. Col., MC, AUS)
 Charles H. Armentrout, Asheville, N. C. (Lt. Comdr., MC, USNR)
 Robert E. Driscoll, Chicago, Ill. (Capt., MC, AUS)
 Albert M. Eaddy, Columbia, S. C. (Major, MC, AUS)
 Angelo S. Geraci, Chicago, Ill. (Major, MC, AUS)
 Mack L. Gottlieb, New York, N. Y. (Comdr., MC, USNR)
 Albert S. Hyman, New York, N. Y. (Capt., MC, USNR)
 Clyde H. Kelchner, Allentown, Pa. (Major, MC, AUS)
 Norman Learner, Philadelphia, Pa. (Major, MC, AUS)
 Harris V. Lilga, Petoskey, Mich. (Major, MC, AUS)
 Murlin P. Merryman, Rapid City, S. D. (Major, MC, AUS)
 William C. Munly, Portland, Ore. (Col., MC, USA)
 Frazier J. Payton, Miami Beach, Fla. (Comdr., MC, USNR)
 Heyes Peterson, Wheeling, W. Va. (Lt., MC, USNR)
 Wilfrid E. Riddolls, Brantford, Ont., Can. (Lt. Col., RCAMC)
 Elmer S. Robertson, Richmond, Va. (Major, MC, AUS)
 Robert B. Rutherford, Peoria, Ill. (Col., MC, AUS)
 George C. Thomas, Chevy Chase, Md. (Rear Admiral, MC, USN)
 Ray Vander Meer, Grand Rapids, Mich. (Major, MC, AUS)
 Samuel J. Weinberg, Los Angeles, Calif. (Major, MC, AUS)
 Jack Wexler, Boston, Mass. (Major, MC, AUS)
 Andrew Yeomans, Baltimore, Md. (Comdr., MC, USNR)

ELECTIONS TO MEMBERSHIP, AMERICAN COLLEGE OF PHYSICIANS

On October 20, 1946, on the recommendation of the Committee on Credentials, the Board of Regents formally elected the following candidates to membership. (73 FELLOWS, indicated in full CAPITALS; 126 Associates, indicated in lower case).

Abels, Jules C., New York, N. Y.
 ALLEN, IRENE VIOLA, East St. John, New Brunswick, Can.
 Anday, George John, Chicago, Ill.
 Anthony, Eleanor Margaret, Philadelphia, Pa.

ARNETT, SAMUEL CULLEN, JR., Lubbock, Tex.
 Avey, Harry Thompson, Jr., Oklahoma City, Okla.
 Balberor, Harry, Detroit, Mich.
 BARTON, EVAN MANSFIELD, Chicago, Ill.
 Bass, Hyman Elihu, New York, N. Y.
 Bates, Clarence Edgar, Oklahoma City, Okla.
 BERNSTEIN, ARTHUR, Chicago, Ill.
 BEST, GORDEN NEWALL, Council Bluffs, Iowa
 Beyer, Karl Henry, Jr., Bala-Cynwyd, Pa.
 Blumenthal, Basil, Washington, D. C.
 Boger, William Pierce, Philadelphia, Pa.
 BOLAND, EDWARD WARD, Los Angeles, Calif.
 Boone, Leslie Jay, Washington, Pa.
 Borson, Harry J., Berkeley, Calif.
 Bosworth, Edward Louis, Rome, Ga.

Branch, Charles Henry Hardin, Philadelphia, Pa.
 Brandsma, Maynard, Beverly Hills, Calif.
 Branning, William Sterry, Durham, N. C.
 Brightman, I. Jay, Albany, N. Y.
 Brooks, Nathan, Detroit, Mich.
 BROSIN, HENRY WALTER, Chicago, Ill.
 Brown, Jesse Benjamin, Ancon, C. Z.
 Budnitz, Joseph, Pittsfield, Mass.
 BUTLER, STUYVESANT, Winnetka, Ill.

CANDEL, SAMUEL, Brooklyn, N. Y.
 CARROLL, HOWARD BERTRAM, Chicago, Ill.
 Chanis, Rolando Augusto, Panama, R. P.
 Chatard, Ferdinand Edme, (MC), USN, Washington, D. C.
 Cherry, Clifford Burns, Los Angeles, Calif.
 Christman, Herbert Emanuel, Lakewood, Ohio
 Closterman, Donald Franks, Kingston, Pa.
 COGGESHALL, LOWELL THELWELL, Chicago, Ill.
 Colvin, Merl G., Williamsport, Pa.
 Corrado, Albert Guy, Pittsburgh, Pa.
 Cotter, Edward Francis, Baltimore, Md.
 CRAGO, FELIX HUGHES, Great Falls, Mont.
 CRAIN, DARRELL CLAYTON, Washington, D. C.
 Crumrine, Clarence Acklin, Washington, Pa.

Danowski, Thaddeus Stanley, New Haven, Conn.
 DAVIS, JOHN PRESTON, Winston-Salem, N. C.
 Dick, Macdonald, Durham, N. C.
 Dobson, Herbert Victor, Peterborough, Ont., Can.
 Doty, Edwin John, New York, N. Y.
 DUNN, THOMAS BALFOUR, Oakland, Calif.
 DUNN, WILLIAM LeROY, Washington, D. C.

ECHIKSON, JOSEPH ISRAEL, Newark, N. J.
 ENGLISH, JOHN PAUL, South Bend, Ind.
 Evans, Carvel Swift, Salt Lake City, Utah
 EVANS, ELWYN, Winter Park, Fla.

Fairchild, Laurence McCarty, Ancon, C. Z.
 FISHER, H(ARRY) RUSSELL, Bala-Cynwyd, Pa.
 Fisher, Saul H., New York, N. Y.
 Florio, Lloyd Joseph, Denver, Colo.
 Ford, Elbert Sylvester Caldwell, Philadelphia, Pa.
 Forte, Joseph Anthony, Jr., (MC), USN, Washington, D. C.
 Fox, Theodore T., New York, N. Y.
 Freeman, Joseph, Philadelphia, Pa.
 Freireich, Kal, Forest Hills, N. Y.
 FRENCH, A(DAM) JAMES, Ann Arbor, Mich.
 Friedman, Gerald Jonas, New York, N. Y.

Gendel, Benjamin Robert, New Haven, Conn.
 GETTELFINGER, WILFRID CHARLES, Louisville, Ky.
 GILL, CHARLES CHUTE, (MC), USA, Washington, D. C.

Gillick, Frederick George, Willow Grove, Pa.
GILMAN, ROBERT LOUIS, Wallingford, Pa., (MC), USNR
Goldhamer, Morton Louis, Cleveland, Ohio
GRAHAM, ROBERT WILLIAMS, Toronto, Ontario, Can.
Greenberg, Samuel U., New York, N. Y.
GUTHRIE, MORRIS BAKER, Columbus, Ohio

Hammel, Max Arthur, Santa Barbara, Calif.
Hartnett, William Gordon, Muskogee, Okla.
Harvey, Joseph Paul, Youngstown, Ohio
HAYS, JAMES FRANKLIN, (MC), USN, Washington, D. C.
Henry, Blondy Sewell, Memphis, Tenn.
HERNANDEZ, VINCENT, (MC), USN, Washington, D. C.
Hilker, Albert William, Eau Claire, Wis.
HOLLANDER, JOSEPH LEE, Philadelphia, Pa.
HOLMAN, CHARLES NIXON, Portland, Ore.
Horwitz, Orville, Philadelphia, Pa.

IRVINE, JED HOTCHKISS, New York, N. Y.
Issos, Demetrios Nestor, Birmingham, Ala.
Jenkins, Daniel Edwards, Ann Arbor, Mich.
JENNINGS, HARRY NELSON, Calgary, Alberta, Can.
Johnson, Carl Harold, Gettysburg, Pa.
Josephs, Irving Louis, Los Angeles, Calif.
Joslyn, Harold Lees, St. Louis, Mo.

Kapp, Louis A., New York, N. Y.
Kaufman, Paul, New York, N. Y.
KEENEY, EDMUND LUDLOW, Baltimore, Md.
KENNEDY, J(AMES) ALLEN, Nashville, Tenn.
Keyes, John Wesley, Detroit, Mich., (MC), AUS
KLEEFIELD, ELMER ALFRED, Forest Hills, N. Y.
KNEEDLER, WILLIAM HARDING, Philadelphia, Pa.
Kohl, Harold Willis, Tucson, Ariz.
Kostal, Otto Albin, Hastings, Nebr.
KUBANEK, JOSEPH LOUIS, Ely, Mich.
KWITNY, ISADORE JACOB, Indianapolis, Ind.

LaDUE, JOHN SAMUEL, New York, N. Y.
LANDAU, FREDERICK LOUIS, JR., Bronxville, N. Y.
Langendorf, Richard, Chicago, Ill.
Layman, Leslie Holmes, Louisville, Ky.
LEGER, LEE HERMAN, Kansas City, Kan.
LEHNHOFF, HENRY JOHN, JR., Omaha, Nebr.
Leming, Howell Elijah, Fayetteville, Ark.
LEONARD, CHARLES EDWARDS, Oklahoma City, Okla.
Livingston, A. Edward, Bloomington, Ill.

Magee, Conway Stone, Lake Charles, La.
Mallach, Joseph Francis, Chicago, Ill.
MANNING, ISAAC HALL, JR., Durham, N. C.
Mattingly, Thomas William, (MC), USA, Washington, D. C.
McCombs, (Annie) Parks, New York, N. Y.

Mensh, Maurice, Washington, D. C.
 Miller, Edward Bernard, New York, N. Y.
 Miller, Harry Irwin, Pittsburgh, Pa.
 MODELL, WALTER, New York, N. Y.
 Montgomery, Max Malcolm, Chicago, Ill.
 Moore, Matthew Thibaud, Philadelphia, Pa.
 MURPHY, PAUL, St. Louis, Mo.
 Musser, Marc James, Jr., Madison, Wis.

Nayer, Herman R., New York, N. Y.
 Nelson, James David, Spartanburg, S. C.
 Nelson, Oscar Louis Norman, Minneapolis, Minn.
 NICHOLSON, WILLIAM McNEAL, Durham, N. C.

Oren, Benjamin Gershwin, Miami, Fla.

PETERS, GUSTAVUS ALFRED, Rochester, Minn., (MC), AUS
 PETERS, MICHAEL, Telford, Pa.
 Phelps, James Everett, Paterson, N. J.
 Pohle, Frederick John, Madison, Wis.
 Province, William Ditmars, Franklin, Ind.

Redisch, Walter, Jackson Heights, N. Y.
 Reifenstein, George Henry, Syracuse, N. Y.
 Reitman, Norman, New Brunswick, N. J.
 Rivers, Daniel Christopher, Cincinnati, Ohio
 Robins, Arthur Benjamin, New York, N. Y.
 Robinson, Murry Myer, Washington, D. C.
 ROPER, WILLIAM HAMILTON, Sanatorium, N. C., (MC), AUS
 Rosenkrantz, Jacob Alvin, New York, N. Y.
 ROTKOW, MAURICE JULIAN, Des Moines, Iowa
 RUSKIN, ARTHUR, Galveston, Tex.

SAPERO, JAMES JOSEPH, (MC), USN, Washington, D. C.
 SCARLETT, EARLE PARKHILL, Calgary, Alberta, Can.
 Schoemperlen, Clarence Benjamin, Winnipeg, Manitoba, Can.
 Schwade, Edward David, Milwaukee, Wis.
 SCHWARTZ, WALTER HENRY, (MC), USN, Washington, D. C.
 SENECA, HARRY TUNE A., New Orleans, La.
 SHAFFER, CARL FRANCIS, Houston, Tex.
 Shapiro, Herman Harvey, Madison, Wis.
 Sharp, Reuben Lore, Camden, N. J.
 Shuey, Charles B., Dallas, Tex.
 Sikkema, Stella Hazen, Madison, Wis.
 Silbermann, Isador, New York, N. Y.
 Simonart, Pierre Charles, Philadelphia, Pa.
 Sims, John LeRoy, Madison, Wis.
 SKINNER, ROBERT BARRETT, (MC), USA, Washington, D. C.
 Sloan, Norman Rose, Kalaupapa, Molokai, T. H.
 Smith, Jasper Archer, Waterbury, Conn.
 SMITH, JEROME FROST, (MC), USN, Washington, D. C.
 Smith, Sol (omon), Baltimore, Md.
 SOLEM, GEORGE OLIVER, Chicago, Ill.

Sorkin, S. Zelig, New York, N. Y.
 STARR, (MERRITT) PAUL, Pasadena, Calif.
 Steinberg, David Louis, Elgin, Ill.
 Stellar, Lawrence Irving, Boston, Mass.
 Stewart, Donald William Wright, Sudbury, Ontario, Can.
 STEWART, WILLIAM CRAWFORD, Charleston, W. Va.
 STONE, CHARLES FREDERIC, JR., Atlanta, Ga.
 Stone, Frederick James, Buffalo, N. Y.
 Sullivan, Clement Joseph, St. Louis, Mo.
 SUNDERMAN, F(REDERICK) WILLIAM, Philadelphia, Pa.

Taylor, William Wood, Memphis, Tenn.
 Thomas, Caroline Bedell, Baltimore, Md.
 Thomas, Sydney Frissell, Menlo Park, Calif.
 Thompson, James Harwood, San Francisco, Calif.
 Thompson, William Taliaferro, Jr., Richmond, Va.
 Tracey, Martin L., Needham, Mass.
 Trawick, John David, Jr., Louisville, Ky.

VOEGTLIN, WALTER LYLE, Seattle, Wash.

WAKEMAN, DON CONKLIN, Topeka, Kan.
 Warburton, Ralph Thomas, North Canton, Ohio
 WARRICK, GEORGE WILKS, Birmingham, Ala.
 WARSHAWSKY, HARRY, Dayton, Ohio
 Weiner, Joseph G., Philadelphia, Pa.
 WHITE, ARTHUR EUGENE, (MC), USA, Washington, D. C.
 WHITE, ASHER ABBOTT, Minneapolis, Minn.
 WHITE, MAJOR SAMUEL, (MC), USA, Washington, D. C.
 WILLETT, FORREST MUNROE, San Francisco, Calif.
 Williams, Leonard David, Plainfield, N. J.
 WILSON, CHARLES PEARSON, Portland, Ore.
 Wilson, Joseph McMilton, Dayton, Ohio
 Wilson, Rex Hamilton, Akron, Ohio
 Wirts, Charles Wilmer, Jr., Philadelphia, Pa.
 Wolfman, Benjamin H., USPHS, Washington, D. C.
 Wolpaw, Ralph, Cleveland, Ohio

Yarmy, Milton Marvin, Youngstown, Ohio

Zolov, Benjamin, Portland, Maine

James A. Halsted, M.D., F.A.C.P., has been appointed Chief of the Medical Service of the Faulkner Hospital, Jamaica Plain, Boston, to succeed Channing Frothingham, M.D., F.A.C.P., who has reached the retiring age.

Dr. Halsted is a graduate of the Harvard Medical School and received his intern and resident training at the Massachusetts General Hospital and the Lakeside Hospital in Cleveland. He is a diplomate of the American Board of Internal Medicine and a member of the American College of Physicians. He holds the rank of Assistant Physician at the Massachusetts General Hospital. Dr. Halsted was overseas with the 6th General Hospital and on his discharge held the rank of Lieutenant Colonel. He was awarded the Legion of Merit. Dr. Halsted practices internal medicine in Dedham.

OBITUARIES

DR. WILLIAM SCHAEFFER BERTOLET

William Schaeffer Bertolet, M.D., F.A.C.P., was born in Oley, Berks County, Pennsylvania, in 1875. He attended Keystone State Normal School at Kutztown, and Franklin and Marshall College of Lancaster. He graduated from the University of Pennsylvania School of Medicine in 1900. At one time he was assistant to the late Dr. Judson Daland, F.A.C.P., of Philadelphia. For several years he was Pathologist at the Reading Hospital, thereafter becoming Chief of the Medical Service and Medical Director. He was formerly President of the Berks County Medical Society; a member of the Reading Medical Society, the Pennsylvania State Medical Society, the American Medical Association; a Fellow of the American College of Physicians since 1923; and a Diplomate, American Board of Internal Medicine.

Dr. Bertolet was one of the leaders in the field of Internal Medicine in the Eastern part of Pennsylvania. He died on October 9, 1946. His passing will be mourned by a large number of patients and a wide circle of distinguished friends.

E. L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. MATHEW ARNOLD SPANGELBERGER

Mathew Arnold Spangelberger, M.D., F.A.C.P., was born in New Albany, Indiana, in 1880, where he lived until entering the University of Louisville for his premedical training. After graduation with the M.D. degree from the Denver and Gross College of Medicine in 1904, he began practice in Denver and continued active until shortly before his death on June 9, 1946, at the age of 66.

Dr. Spangelberger was a prominent figure in Colorado Medicine throughout his active professional life. He was particularly active as a consultant in Internal Medicine upon the staff of Saint Anthony's Hospital, twice serving as president. He also held appointments upon the staffs of St. Luke's, Children's, St. Joseph's, Denver General and Mercy Hospitals. He was director for many years of the diagnostic division of the Ave Maria Clinic, and in spite of failing health he assumed heavy war-time teaching duties in the Outpatient Department of the University of Colorado School of Medicine. Dr. Spangelberger spent frequent periods in postgraduate study at such institutions as the Harvard, Northwestern, Chicago Postgraduate, and New York Postgraduate Medical Schools. He was a member of the Denver County and Colorado State Medical Societies, the American Heart Asso-

ciation and a Fellow of the American Medical Association and the American College of Physicians, the latter since 1931.

WARD DARLEY, M.D., F.A.C.P.,
Governor for Colorado

DR. JOSEPH E. SCOTT

Joseph Eckles Scott, M.D., F.A.C.P., died in Portland, Oregon, on April 23, 1946, at the age of 32. Dr. Scott was born on October 14, 1913, in Portland. He graduated from Willamette University in Salem with a B.A. degree in 1935. Following this he entered the University of Oregon Medical School, receiving the M.A. degree in Biochemistry in 1937 and the M.D. degree in 1941. He was a member of Sigma Xi and Alpha Omega Alpha. He completed an internship in 1942 and served a residency in Medicine at the University of Oregon Medical School Hospitals and Clinics from July 1, 1942 to December 31, 1943.

Dr. Scott was associated with Dr. Blair Holcomb in the practice of medicine until he entered practice by himself in November, 1945. He was an Instructor in Medicine at the University of Oregon Medical School and a member of the staff of Good Samaritan Hospital.

Dr. Scott was highly respected by the medical profession and his loss will be keenly felt.

D. W. E. BAIRD, M.D., F.A.C.P.

DR. CHAMPNEYS HOLT HOLMES

Dr. Champneys Holt Holmes, 52, a Fellow of the American College of Physicians since 1937, died June 12, 1946, in a private hospital in Jacksonville, Florida.

Dr. Holmes, a well known chest specialist, who had been in private practice in Atlanta, Georgia, since 1922, retired from active practice in July, 1945, and had been living at Atlantic Beach, Florida. He had been a member of the staff of the Atlanta Tuberculosis Association since 1922 and formerly was President of that group. In 1938-9 he served as President of the American College of Chest Physicians. He was also a member of the American Academy of Tuberculosis Physicians, Georgia State Medical Society, Fulton County Medical Society, American Medical Association, Southern Medical Association, National Tuberculosis Association, Southern Tuberculosis Conference, and the Federation of American Sanatoria. He was the author of numerous published articles on chest diseases. Dr. Holmes received his medical degree from the Johns Hopkins University School of Medicine in 1919.

GLENVILLE GIDDINGS, M.D., F.A.C.P.,
Governor for Georgia

DR. PAUL FORREY STOOKEY

Paul Forrey Stookey, M.D., F.A.C.P., died November 25, 1945. Dr. Stookey became a Fellow of the American College of Physicians in 1936.

Dr. Stookey was born in Cedar Rapids, Iowa, September 17, 1888. He received the M.D. degree in 1913 from the Chicago College of Medicine and Surgery and subsequently undertook postgraduate studies at the University of Minnesota and the University of Vienna.

Dr. Stookey was a member of the Jackson County Medical Society, Kansas State Medical Society, Kansas City Southwest Clinical Society, Kansas City Academy of Medicine, Mississippi Valley Dermatological Society, and Southern Medical Association; and was a Fellow of the American Medical Association.

Dr. Stookey held appointment at the University of Kansas School of Medicine as Associate Professor of Contagious Medicine, and at the Kansas City Western Dental College as Professor of Immunology and Head of the Department of Experimental Medicine. He served as Senior Consulting Physician and Director of Services, Isolation Department, Municipal Hospital of Kansas City; and as Attending Physician, at St. Mary's, St. Joseph, and Research Hospitals.

DR. HAROLD EUGENE ROBERTSON

Harold Eugene Robertson, A.B., M.D., F.A.C.P., Rochester, Minn., died March 8, 1946.

Dr. Robertson was born in Waseca, Minn., October 8, 1878. He attended Carleton College and studied medicine at Columbia University and the University of Pennsylvania, receiving the degree of Doctor of Medicine from the latter school in 1905. His postgraduate studies were conducted at the University of Berlin and the University of Freiburg. After appointments as Instructor in Pathology at the Albany Medical College and the Harvard Medical School, Dr. Robertson joined the Faculty of Medicine of the University of Minnesota and rose to the position of Professor of Pathology and Director of the Department of Pathology, Bacteriology, and Public Health. He also served as Professor of Pathology in the University's Graduate School, Mayo Foundation, and as Head of the Section on Pathologic Anatomy of the Mayo Clinic.

Dr. Robertson was a member of Phi Beta Kappa, Sigma Xi, Olmsted County Medical Society, Minnesota State Medical Association, Minnesota Academy of Medicine, Society for Experimental Biology and Medicine, Minnesota Pathologic Society, and Federation of American Societies for Experimental Biology. He was a past President of the American Association of Pathologists and Bacteriologists, and of the International Association of Medical Museums. Dr. Robertson, a Fellow of the American Medical Association and, since 1920, of the American College of Physicians, at one

time held the position of Director of the American Society for the Control of Cancer.

Dr. Robertson served as a Major in the Medical Corps of the American Expeditionary Forces during World War I, and was on inactive duty during World War II.

DR. MAURICE ALEXANDER KUGEL

Maurice Alexander Kugel, A.B., M.D., (Associate), died early in March, 1946, at Miami Beach, Fla.

Dr. Kugel was born in Russia, August 4, 1899, and came to this country at an early age. He attended Harvard College and the Yale University Medical School, graduating from the latter in 1926. His postgraduate work was done in Berlin, Hamburg and Prague. He served on the staffs of the Mt. Sinai and Beth Israel Hospitals, New York, N. Y.

In 1936 Dr. Kugel removed to Miami Beach, Fla., and has since served on the staffs of St. Francis Hospital and the National Children's Cardiac Home, of which he was Medical Director. He was a member of the Dade County Medical Society, Florida State Medical Association, and the American Heart Association, and a Fellow of the American Medical Association. He was also a past President of the Miami Heart Association. Dr. Kugel became an Associate of the American College of Physicians in 1942.

DR. MURRAY BURNES GORDON

Murray Burnes Gordon, M.D., F.A.C.P., of Brooklyn, N. Y., died June 29, 1946. Dr. Gordon was born in Russia, July 4, 1886. He attended the Long Island College Hospital and graduated in 1908 with the degree of Doctor of Medicine. He held an appointment as Professor of Clinical Pediatrics in the Long Island College of Medicine from 1930 until his demise, and as Clinical Professor of Pediatrics in New York Polyclinic Medical School and Hospital from 1937 on. He held hospital appointments as Attending Pediatrician and Endocrinologist at the Israel-Zion Hospital, Brooklyn; Visiting Physician, Kingston Avenue Hospital, Brooklyn; Consulting Pediatrician, Rockaway Beach Hospital and Dispensary and Infants Home, Brooklyn. Dr. Gordon became Chief of the Endocrine Clinic of the Long Island College Hospital in 1923.

Dr. Gordon was a member of the Kings County Medical Society, Brooklyn Pediatric Society, Associated Physicians of Long Island, Medical Association of Greater New York, Medical Association of the State of New York, Association for the Study of Internal Secretions and a Fellow of the American Medical Association. Dr. Gordon was a prolific writer of papers dealing with topics in his chosen field of endocrinology. He was a diplomate of the American Board of Pediatrics. Dr. Gordon became a Fellow of the American College of Physicians in 1919.

DR. MARR BISAILLON

Marr Bisailon, M.D., F.A.C.P., Portland, Ore., died June 3, 1946 at the age of 63. Dr. Bisailon was born in 1882 in Minneapolis, Minn. He received his M.D. degree from the University of Oregon Medical School in 1911. He became a member of the faculty of his alma mater and held for many years the position of Assistant Clinical Professor of Medicine. He was Co-medical Director, Portland Open Air Sanatorium; member of the staffs of Multnomah and St. Vincent's Hospitals. Dr. Bisailon was a member of the North Pacific Society of Internal Medicine, Portland Academy of Medicine, Portland City and County Medical Society and the Oregon State Medical Society. He was a Fellow of the American Medical Association. A diplomate of the American Board of Internal Medicine, Dr. Bisailon became a Fellow of the American College of Physicians in 1921.

DR. FRED M. SMITH

Fred M. Smith, M.D., F.A.C.P., was born in Yale, Jasper County, Illinois, May 31, 1888. He received his B.S. degree from the University of Chicago in 1913; M.D., Rush Medical College, Chicago, 1914; intern, Presbyterian Hospital, Chicago, 1914-1916; Associate in Medicine, 1918-1920; Instructor in Medicine, 1920-1923 and Assistant Professor of Medicine, 1923-1924, Rush Medical College; Professor and Head, Theory and Practice of Medicine, State University of Iowa, 1924-1946.

Dr. Smith was Assistant Attending Physician, Presbyterian Hospital, Chicago 1918-1924; Attending Physician, Evanston Hospital, 1923-1924. Physician-in-Chief, University Hospital, State University of Iowa, 1924-1946.

Dr. Smith was a member of the Chicago Society of Internal Medicine, Chicago Institute of Medicine, Central Society for Clinical Research, Society of Experimental Biology and Medicine, American Physiological Society, Association of American Physicians and Vice-President of the American Society for Clinical Investigation.

Dr. Smith was a Fellow of the American College of Physicians since 1930 and College Governor for the State of Iowa, 1939-1942; Chairman of Section on Practice of Medicine, American Medical Association; Editor-in-chief, "American Heart Journal"; Diplomate, American Board of Internal Medicine. He wrote the section on diseases of the heart in Musser's "Internal Medicine."

Dr. Smith was fortunate in being associated with Dr. James B. Herrick when the early work on the clinical diagnosis of coronary thrombosis was being done. He showed that experimental myocardial infarction induced in dogs by coronary artery ligation resulted in electrocardiographic patterns similar to those in Herrick's cases. His interest and studies then extended to many other phases of coronary artery disease, the general fields of cardi-

ology and internal medicine. He represented a happy combination of investigator, clinician and teacher. His many friends throughout the country join his family in mourning their great loss.

Five years ago he suffered an attack of the condition to which he devoted much study, coronary thrombosis. Although he curtailed his work somewhat thereafter, he remained actively at work. On February 23, 1946 he had a fatal second attack.

BENJAMIN F. WOLVERTON, M.D., F.A.C.P.,
Governor for Iowa

DR. FRANK MANLY FULLER

Frank Manly Fuller, A.B., M.A., M.D., F.A.C.P., Keokuk, Iowa, died March 19, 1946, at the age of 77. He was born in Keokuk, September 29, 1868. He attended Parsons Academy and Parsons College, Fairfield, Iowa, and graduated in medicine from Keokuk Medical College in 1897. He served on the instructional staff of Keokuk Medical College, 1898-1908; for many years on the staffs of the Graham Protestant Hospital and St. Joseph's Hospital; served as Chairman, Secretary, and member of the Iowa State Board of Medical Examiners; as President and Vice-President of the Federation of State Medical Boards of the United States; as President of the Iowa State Medical Society, of which he was a life member; of the Lee County Medical Society, of the Iowa Clinical Medical Society, of the South-eastern Iowa Medical Society; and of the Des Moines Valley Medical Society. He served during World War I, overseas, as Captain, (M. C.), U. S. A.; served his city as Alderman and as physician to the Board of Health; he was a Fellow of the American College of Physicians since 1920, and was a diplomate of the American Board of Internal Medicine.

Dr. Fuller until his last illness, was an enthusiastic and vigorous student and practitioner of medicine. He was a hard worker in all of the medical organizations of which he was a member, and an eloquent proponent of everything he considered progressive and for the general good. He was much in demand as a consultant in medicine.

His loss will be keenly felt in all the medical organizations in which his face had long been so familiar.

BENJAMIN F. WOLVERTON, M.D., F.A.C.P.,
Governor for Iowa

DR. CHARLES WILSON MILLS

Charles Wilson Mills, A.B., M.D., F.A.C.P., Tucson, Ariz., died September 29, 1945 of coronary occlusion at the age of 66.

Dr. Mills was born at South Williamstown, Mass., September 1, 1879. He attended Williams College and the Johns Hopkins University School of

Medicine, from which he received his M.D. degree in 1908. Choosing tuberculosis as his specialty he had a distinguished career. Following early appointments as Associate Physician, Loomis Sanatorium and Resident Physician, Cragmor Sanatorium, Dr. Mills served as Medical Director, Tucson-Arizona Sanatorium, 1920-21 and of the Tucson Tubercular Charities Hospital, 1921-27. Subsequently he became Associate Medical Director of the Desert Sanatorium and Institute of Research and a member of the staffs of the Southern Methodist and St. Mary's Hospitals.

Dr. Mills was a member and past President of the Pima County Medical Society and a member of the Arizona State Medical Association, National Tuberculosis Association, Southwestern Medical Association and a Fellow of the American Medical Association.

A diplomate of the American Board of Internal Medicine, Dr. Mills became a Fellow of the American College of Physicians in 1929.

DR. TERRANCE CALVIN MOYER

Terrance Calvin Moyer, M.D., F.A.C.P., of Lincoln, Nebraska, died suddenly Sunday, September 8, 1946, following a subacute attack of coronary thrombosis. Dr. Moyer became ill while playing golf at the Lincoln Country Club and died in a hospital a short time later. He was 58 years old.

Dr. Moyer was born in New Berlin, Pennsylvania, March 21, 1888. He was graduated from Union Seminary in New Berlin in 1908, and received his B.A. degree in 1911 and his M.D. degree in 1914 from the University of Nebraska. Dr. Moyer served his internship at Wise Memorial Hospital, Omaha, Nebraska, followed by graduate study at Columbia University. In 1915 he entered practice with his uncle, the late Dr. C. C. Moyer of Lincoln. During World War I he served in the Army Medical Corps at the Base Hospital, Camp Lee, Virginia. He was released from active duty in 1919 with the rank of Captain, and held a Major's commission in the Reserve Corps until 1926. Upon honorable discharge from the Army in 1919, he entered private practice in Lincoln, specializing in internal medicine, his particular interests pointed toward diseases of the lungs. He was a member of the staff of the Bryan Memorial and Lincoln General Hospitals and a lecturer in the school of nursing.

Dr. Moyer was President of the Lancaster County Tuberculosis Association, a Fellow of the American Medical Association, the American College of Chest Physicians, and of the American College of Physicians since 1934; a Diplomate of the American Board of Internal Medicine, member of the American Trudeau Society, the American Heart Association, National Tuberculosis Association, and the Association for the Study of Internal Secretions. He was also a member of the American Legion Lincoln Post Number Three and belonged to the Last Man's Club. He was a Scottish Rite Mason, member of the Shrine, the Royal Order of Jesters and the Lions

Club, and a past president of the Zodiac Club. His fraternities were Sigma Alpha Epsilon and Nu Sigma Nu.

Dr. Moyer was untiring in his professional work, the welfare of his patients always being his uppermost thought. His pleasing and sparkling personality and his wide interests, first in his profession and then in outdoor life, gained for him the love and respect of his confreres, his patients and his friends. He was an enthusiastic fisherman and cameraman, and kept a photographic record of his outdoor activities. He took great pride in his farms and their development, and hoped to retire to one of his farms in Pennsylvania near his birthplace.

Dr. Moyer is survived by his wife, the former Minerva Fuller, and two daughters, Mrs. Claude S. Wilson, Jr., of Boulder, Colorado, and Jo Ann, who resides at the family home.

Dr. Moyer's passing is a great loss not only to the medical profession but to his patients and friends as well.

J. D. McCARTHY, M.D., F.A.C.P.,
Governor for Nebraska

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EOSINOPHILIA IN MALIGNANT TUMORS: ITS SIGNIFICANCE *

By NORMAN H. ISAACSON, M.D., and PAUL RAPOPORT, M.D.,
Brooklyn, New York

EHRLICH,²⁰ in 1880, was the first to stain and definitely describe the eosinophile, though previous investigators^{29, 30} seem to have recognized the coarse granules in the unstained cells. Ehrlich believed that eosinophiles originated and matured in the bone marrow and were delivered into the circulating blood as a definite cell type. This concept is still considered to be correct.

Most hematologists^{21, 22, 23, 26} today agree that 6 per cent of the total white cell count is the upper limit of normal for eosinophilic leukocytes. Kirk²⁴ recently made an extensive review of the literature on eosinophilia and reported an eosinophile count of over 6 per cent in the following conditions: (1) Allergic diseases of all types. (2) Certain skin diseases, such as mycosis fungoides, dermatitis herpetiformis, pemphigus, etc. (3) Parasitic infestations. Eosinophilia occurs in Hodgkin's disease, leukemia, periarteritis nodosa, benzol poisoning, Simmonds' disease, scarlet fever and Loeffler's syndrome. It has been observed in patients on a raw liver diet and in others after splenectomy.

Another cause of eosinophilia, which is either omitted or scarcely mentioned in modern hematology texts or treatises on the subject, is malignancy. Rheinbach¹ in 1893 was the first to report such a case. His patient had a malignant tumor of the neck and cervical lymph nodes with a white blood cell count of 120,000 cells per cu. mm., 40 per cent of which were eosinophiles. No histological sections of the tumor were taken, but the disease clinically was not leukemia. Since then there have been 18 case reports of eosinophilia with malignancy.† Most of these reports appear in the foreign literature

* Received for publication March 16, 1946.

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† Collins and Kaplan's²⁷ case was omitted since no operation or autopsy report was available to confirm their diagnosis.

and only a few in the American journals. These are listed chronologically in the chart below (table 1).

Many theories as to the cause of eosinophilia in malignant tumors have been advocated. Early investigators^{2,5} attributed it to necrosis of tumor tissue, the products of protein breakdown causing an eosinophylotactic re-

TABLE I
Previous Cases of Eosinophilia in Malignant Tumors

Author	Date	White Count	Eosino- philes	Type of Tumor	Metastases
1. Rheinbach	1893	120,000	40%	Primary site unknown	Cervical lymph nodes
2. Kappis	1907	43-50,000	33-39%	Bronchogenic carcinoma	Regional lymph nodes, ribs and sternum
3. Dunger	1910	35,000	65%	Carcinoma of colon	Lymph nodes, omentum
4. Strisower	1913	15,000	45%	Carcinoma of uterine fundus	Liver, lymph nodes, pleura
5. Czaki	1921	31,200	30%	Carcinoma of colon	Liver, lymph nodes
6. Schellong	1922	16,800	11%	Carcinoma of common bile duct	Liver, lymph nodes
7. Weiss	1926	6-16,000	4-31%	Adenocarcinoma of stomach	No metastases, but not ruled out
8. Netchaeff*	1929			Carcinoma of thyroid gland	
9. Pisa	1931	72,000	45%	Sarcoma surrounding the pancreas	Lymph nodes, liver, spleen
10. Roca de Viñals*	1931			Epithelioma of penis	
11. Chiray and Baudouin	1931	7-26,000	19-70%	Carcinoma of head of pancreas	Lymph nodes, liver
12. Sterling and Okumewski*	1932			Carcinoma of uterine cervix	
13. Paviot, Levrat and Guichard	1935	90,000	74%	Perirenal reticulosarcoma	Throughout abdomen
14. Riopelle	1936	10-15,000	62%	Pancreatic carcinoma (?)	Liver, lymph nodes, lungs
15. Sala and Stein	1937	18-36,000	52-70%	Carcinoma of uterine cervix	Adnexa, lymph nodes
16. Basnueno, Suttar and Portella*	1937			Carcinoma of penis	
17. Morgan and Ballinger	1938	21-40,000	1-17%	Primary site unknown	Liver
18. LaManna and Borghetti	1938	9,000	10%	Fibrosarcoma of face	Skin, muscle, kidney
19. Scheer	1939	not stated	6-53%	Scirrhous gastric carcinoma	Throughout abdomen

* Cases quoted by other authors in foreign journals. Original articles not available in American libraries.

sponse. Others attributed it to bone marrow metastases with consequent stimulation of eosinophile production at that site, although osseous involvement could not be demonstrated in all cases. Strisower⁴ made the startling assertion that the eosinophilia was due to a vagal reflex. His patient had a hepatoma which metastasized to the cervical lymph nodes and compressed

the vagus nerve. The eosinophilia disappeared after removal of the nodes. However, after a brief remission, the eosinophile count again returned to its former level. Paviot¹³ and his co-workers suggested an origin from the connective tissue surrounding the tumor, since local tissue eosinophilia in malignant tumors has been reported many times. They further justify this statement by the finding of mononuclear eosinophilic cells in the blood stream in their case. Pisa⁹ claimed a familial eosinophilic predisposition is necessary to provoke an eosinophilic response to malignant tumors, the foreign protein of the tumor cells being the provocative agent. Weiss,⁷ however, experimentally injected extracts of tumor tissue and of blood from a patient who showed a hypereosinophilia into guinea pigs, rabbits and dogs. In no case was an increase in eosinophiles observed.

In the following pages we wish to report 15 cases of eosinophilia found in a review of 2363 cases of malignancy at the Jewish Hospital of Brooklyn in the last eight years. Included are cases of carcinoma of the breast and adrenal in which eosinophilia has hitherto not been reported.

CASE REPORTS

I. *Bronchogenic Carcinoma: Case 1.* C. L., a 70 year old white male, was admitted to this hospital on October 26, 1945 with colicky epigastric pain of three weeks' duration and jaundice for one week. On admission he was jaundiced, acutely ill and disoriented. He presented bilateral painless anterior and posterior cervical lymphadenopathy. The lungs were clear, the abdomen distended, with shifting dullness, and a fluid wave present. There were ecchymoses over the chest and extremities and bleeding gums. The stools were tarry.

A blood count done at home showed 80,000 white blood cells of which 18 per cent were eosinophiles. On admission to the hospital he had a hemoglobin of 84 per cent, red blood cells 4.6 million per cu. mm., white blood cells 120,000 per cu. mm. with 44 polymorphonuclears, 26 band forms, 3 myelocytes, 2 lymphocytes, 1 monocyte and 24 eosinophiles. The platelets were diminished. The following day his white blood cell count had increased to 140,000 per cu. mm. with 32 per cent eosinophiles. Stool examinations were reported as negative for ova and parasites on three occasions. A tentative diagnosis of eosinophilic leukemia was made, but before bone marrow studies could be done the patient died.

At autopsy, the patient had a carcinoma of the eparterial branch of the right upper lobe bronchus with metastases in the cervical, supraclavicular, axillary, inguinal, tracheobronchial, posterior mediastinal, retroperitoneal and mesenteric lymph nodes. There were metastatic nodules in the liver, kidneys and thyroid gland. There were diffuse metastases to the vertebral column and microscopic metastases in the spleen. Necrosis was present in all the tumor nodules, but tissue eosinophilia in the region of the tumor was not demonstrable.

II. *Carcinoma of the Gall-Bladder: Case 2.* G. B., a 55 year old white female, entered this hospital on July 5, 1938, complaining of pain in the right lumbar region of four months' duration. The positive physical findings were a moderate hypertension and a firm tubular mass palpable in the right upper quadrant. Oral and intravenous cholecystography was performed but failed to visualize the gall-bladder. Jaundice first appeared on July 31 and an exploratory operation was carried out four days later. At operation an indurated mass was found in the fundus of the gall-bladder and a firm umbilicated nodule in the right lobe of the liver. A cholecystostomy was per-

formed. The patient grew progressively worse post-operatively. On August 25 she vomited 1500 c.c. of blood, went into shock, and died. Autopsy revealed carcinoma of the gall-bladder with metastases in the lymph nodes, and liver and gastric ulcer with hemorrhage. No metastases to bone were demonstrable. The tumor showed slight necrosis but no eosinophilic infiltration. Her blood counts in the hospital averaged 6,000 leukocytes per cu. mm. with 11 per cent eosinophiles.

III. *Carcinoma of the Head of the Pancreas: Case 3.* F. H., a 57 year old colored male, was admitted to this hospital on August 9, 1939 with a history of clay colored stools for one month, icterus of skin and mucous membranes and dark brown urine for three weeks and a 20 pound weight loss during the two weeks prior to admission. Physical examination confirmed the presence of jaundice, and a nodular liver was palpated four fingers' breadth below the xiphoid process. At exploratory laparotomy on August 22, a firm irregular mass was found in the head of the pancreas with several metastatic nodules distributed throughout the liver. A cholecysto-duodenostomy was performed. The post-operative course was uneventful, and the patient was discharged on September 10, 1939. There was no follow-up. His white blood cell counts in the hospital averaged 11,000 per cu. mm. with 11 per cent eosinophiles.

Case 4. G. L., a 59 year old white female, was first admitted to this hospital in June 1938 because of sudden onset of headache and vomiting. She had slight nuchal rigidity and increased reflexes in the lower extremities. A spinal tap was performed and the spinal fluid contained many red blood cells. A diagnosis of subarachnoid hemorrhage was made. At this time she had a white blood cell count of 5300 per cu. mm. with 8 per cent eosinophiles. After three weeks of hospitalization she was discharged improved.

She was readmitted in September 1938 because of recurrence of headache. No abnormal neurological findings were present at this time. A white blood cell count showed 6200 per cu. mm. with 10 per cent eosinophiles. She left the hospital after one week without a further diagnosis being made. One week later, while at home, she began to complain of abdominal cramps. A gastrointestinal series done at this time showed an increased duodenal sweep indicative of enlargement of the head of the pancreas. Shortly thereafter her liver became enlarged and nodular, and ascites developed. Roentgenograms of the lungs and spine showed multiple metastatic nodules in both. Finally in February 1939 she developed numbness and weakness of the right side of the body and lapsed into coma. Her blood count on this last admission showed 5700 leukocytes per cu. mm. with 12 per cent eosinophiles. She died February 27, 1939. No autopsy was obtained.

IV. *Carcinoma of the Colon: Case 5.* A. W., a 41 year old white male, was admitted on August 9, 1945 complaining of right upper quadrant pain of seven weeks' duration. A tender liver was palpable just below the costal margin. Barium enema and a gastrointestinal series were negative, as was a digital rectal examination. His liver increased in size and became nodular. Increasing jaundice developed. At exploratory laparotomy on August 24, a firm fixed mass was palpable high in the rectum with metastatic nodules in the liver, omentum and regional lymph nodes. Biopsy of a liver nodule confirmed the diagnosis of carcinoma. His white blood cell counts in the hospital averaged 19,000 per cu. mm. with 12 per cent eosinophiles.

Case 6. N. K., a 62 year old white female, was admitted to this hospital on June 11, 1940 complaining of obstipation, abdominal distention and pain in the abdomen and back for nine days. Barium enema revealed an annular constricting lesion of the sigmoid colon. After decompression with a Miller-Abbott tube a first stage Mickulicz operation was performed. A constricting adenocarcinoma of the sigmoid colon was found with metastases in all the mesenteric lymph nodes. Histologic examination of the tumor showed necrosis but no eosinophilic infiltration. Her white blood cell counts in the hospital averaged 11,000 with 14 per cent eosinophiles. After 56 days in the hospital she was discharged. There was no follow-up.

Case 7. P. C., a 34 year old white female, entered the hospital on March 26, 1944 complaining of a lump in the right breast of one year's duration and epigastric pain for four months. She had had two previous admissions to this hospital, and her blood counts then showed no eosinophilia. On this admission she had a palpable mass in the right lower quadrant, and a barium enema revealed a napkin ring defect of the hepatic flexure. At operation this was found to be a carcinoma of the hepatic flexure with metastases in the regional lymph nodes. Necrosis and eosinophilic infiltration were both present in the tumor. A resection and primary anastomosis were performed. The lump in the breast was removed and this proved to be a fibroadenoma. Her blood counts on this admission averaged 8000 leukocytes per cu. mm. with 14 per cent eosinophiles. She was discharged. There was no follow-up.

Case 8. H. W., a 40 year old white female, entered the hospital on May 23, 1941 complaining of abdominal cramps, alternating diarrhea and constipation and bleeding per rectum, all for six weeks, with a weight loss of 10 pounds in the past four weeks. A mass was palpable rectally. On May 26, a perineal resection was performed, and microscopic examination of the mass removed confirmed the diagnosis of carcinoma. No necrosis or tissue eosinophilia was present. No evidence of metastases could be found in the limited operative field. Her white blood cell counts averaged 9000 per cu. mm. with 10 per cent eosinophilia. There was also a basophilia of 2 to 6 per cent. Two previous hospital admissions for other complaints showed no eosinophilia higher than 2 per cent. The patient was discharged 14 days post-operatively. There was no follow-up.

Case 9. A. S., a 67 year old white male, was admitted on October 30, 1941 with rectal bleeding of four months' duration. Sigmoidoscopy revealed a firm ulcerated mass in the rectosigmoid, and a barium enema showed a filling defect in this area. On November 9 a Rankin obstructive resection was performed. Metastases had occurred to the pre-aortic lymph nodes but not elsewhere in the abdomen. Microscopic examination of the tumor showed an adenocarcinoma infiltrated with eosinophilic cells. The white blood cell counts averaged 9000 per cu. mm. with 10 per cent eosinophiles.

On April 7, 1942 the patient returned for closure of the colostomy. He was otherwise well. His white blood cell count at this time was 8600 with 1 per cent eosinophiles. There was no further follow-up.

V. Carcinoma of the Stomach: Case 10. R. G., a 42 year old white female, was admitted to this hospital in October 1938 with pallor and weakness but no gastrointestinal complaints. She had a hemoglobin of 27 per cent, a red blood count of 2.78 million per cu. mm., a white blood cell count of 9000 per cu. mm. with no eosinophiles. Gastric analysis revealed no free hydrochloric acid. A gastrointestinal series showed an annular carcinoma in the pyloric region of the stomach. No metastases were noted at operation, at which time a subtotal gastrectomy and gastroenterostomy were performed. Histologic examination of the tumor showed necrosis but no eosinophilia.

The patient was readmitted in September 1939, with jaundice and right upper quadrant pain. The liver was enlarged to three fingers' breadth below the costal margin and was nodular. This time her blood counts showed a normal hemoglobin but a white blood cell count of 15,000 per cu. mm. with 13 per cent eosinophiles. Repeated examinations of the stools for ova and parasites were negative. She refused reexploration and left the hospital against advice on September 29, 1939. There was no follow-up.

VI. Carcinoma of the Breast: Case 11. M. M., a 30 year old white female, was admitted on April 10, 1943 complaining of a painless lump in her left breast with puckering of the overlying skin. A diagnosis of malignancy was confirmed microscopically after a radical mastectomy was performed. No necrosis or eosinophilia

was present in the tumor. Roentgenograms of the chest and long bones showed no demonstrable metastases, and the regional lymph nodes were not involved at operation. The blood counts at this time averaged 8000 leukocytes per cu. mm. with no eosinophiles. Post-operatively she received radiation therapy to her pelvis and an artificial menopause was induced.

She reentered the hospital on October 6, 1943 complaining of bouts of epigastric pain. Her white blood cell counts this time averaged 7500 per cu. mm. with 17 per cent eosinophiles. A gastrointestinal series, barium enema, gastroscopy and bone marrow studies were negative. The stool specimens showed no ova or parasites on repeated occasions. Trichina and echinococcus skin tests were negative. There was no history of allergy. Retrograde metastases to the abdominal lymph nodes were suspected but could not be proved. The patient was discharged without a further diagnosis having been established. There was no follow-up.

Case 12. J. S., a 54 year old white female, entered the hospital in January 1944 with a firm mass in her right breast which had been present for two months. A radical mastectomy was performed and the diagnosis of carcinoma was confirmed on histologic examination. No necrosis or eosinophilia was present in the tumor. The regional lymph nodes were free of metastases. Post-operatively she repeatedly complained of back pain, but roentgen examination of the spine, chest and long bones showed no abnormalities. One count taken in the hospital showed 7900 leukocytes per cu. mm. with 12 per cent eosinophiles.

She was given post-operative roentgen therapy in the out-patient department, and her white blood cell counts there averaged 6000 per cu. mm. with an eosinophilia of 12 to 14 per cent. In April 1944, a roentgenogram of the spine showed metastatic deposits in the lumbar region. She did not return to the clinic and could not be traced.

VII. Adenocarcinoma of the Adrenal Gland: Case 13. B. G., a 50 year old white female, entered the hospital in May 1942 with a prolapsed uterus, cystocele and rectocele. An incidental finding at this time was a palpable mass in the right flank. Intravenous and retrograde pyelography showed distortion of the upper calyces of the right kidney. The abdomen was explored, and a large retroperitoneal mass extending from the dome of the diaphragm to the iliac crest was found. This was removed together with the kidney. The microscopic examination was reported as adenocarcinoma of the adrenal gland without involvement of the kidney. There was extensive necrosis of tumor tissue but no marked infiltration with eosinophilic cells. No intra-abdominal metastases were found at operation. Roentgenograms of the lungs and spine showed no evidence of metastases. Her blood counts averaged 8500 leukocytes per cu. mm. with 12 per cent eosinophiles. The post-operative course was uneventful and she was discharged July 8, 1942.

She was followed in the out-patient department where she repeatedly complained of pain in her incision and generalized aches and pains. Her blood counts repeatedly showed 10 to 16 per cent eosinophilia. On March 6, 1945 a mass the size of a fetal head was found in the right mid-abdomen. Shortly afterward several masses were palpable along the aorta. The liver became enlarged and nodular. Roentgenograms of the chest revealed enlarged mediastinal nodes with metastatic nodules in the right lower and left upper lobes of the lung. The patient is still alive and receiving roentgen-ray therapy. She has lost a great deal of weight and is going rapidly downward. Her last blood count showed 8700 leukocytes per cu. mm. with 16 per cent eosinophiles.

VIII. Metastatic Carcinoma, Primary Site Undetermined: Case 14. J. S., a 69 year old white male, was admitted in January 1940 complaining of upper abdominal pain, constipation and a 20 pound weight loss in the eight weeks prior to admission. The stools showed occult blood on several occasions, but a barium enema and gastrointestinal series were negative. Physical examination showed only a

hypertension of moderate severity. His blood counts revealed an average of 12,000 leukocytes per cu. mm. with 15 per cent eosinophiles. At exploratory laparotomy the liver and omentum were studded with metastatic tumor nodules. Biopsy of the omentum revealed metastatic carcinoma. The patient left the hospital against advice seven days post-operatively and could not be further followed.

IX. *Lymphosarcoma: Case 15.* G. G., a 65 year old white female, entered the hospital on April 21, 1941 with painless swelling of the cervical and axillary lymph nodes of six weeks' duration. On physical examination she presented a moderate hypertension. The liver and spleen were just palpable beneath the costal margins. The peripheral blood showed a white cell count ranging from 9-15,000 per cu. mm. with an eosinophilia of 20 to 32 per cent. Bone marrow studies were normal as were stools for ova and parasites. Biopsy of a cervical node showed lymphosarcoma. The patient received radiotherapy post-operatively and was discharged improved, May 9, 1941. There was no follow-up.

All the above cases are summarized below (table 2).

TABLE II
Chart of Cases from Files of the Jewish Hospital of Brooklyn

Case No.	Type of Tumor	White Blood Cells/cu. mm.	Eosinophiles	Metastases
1	Bronchogenic carcinoma	80-140,000	18-32%	Liver, kidney, spleen, bone, lymph nodes
2	Carcinoma of gall-bladder	6,000	11%	Lymph nodes and liver
3	Carcinoma of pancreas	11,000	11%	Lymph nodes and liver
4	Carcinoma of pancreas	5,500	12%	Liver, lymph nodes, lung, brain, spine
5	Carcinoma of rectum	19,000	12%	Liver, omentum, lymph nodes
6	Carcinoma of colon	11,000	14%	Lymph nodes
7	Carcinoma of colon	8,000	14%	Lymph nodes
8	Carcinoma of rectum	9,000	10%	No metastases
9	Carcinoma of colon	9,000	10%	Lymph nodes
10	Carcinoma of the stomach	15,000	13%	Liver and lymph nodes
11	Carcinoma of the breast	7,500	17%	Lymph nodes?
12	Carcinoma of the breast	8,000	14%	Lumbar vertebrae
13	Adenocarcinoma of the adrenal	8,500	16%	Lymph nodes, lung, liver
14	Metastatic carcinoma, primary site unknown	12,000	15%	Liver and omentum
15	Lymphosarcoma	9-15,000	20-32%	Lymph nodes, spleen and liver involved

DISCUSSION

It should be emphasized that in each case repeated blood counts were made to confirm the presence of eosinophilia and that the eosinophilia was 10 per cent or more of the total white cell count. This was done so that accidental or coincidental eosinophilia could be excluded. With all extraneous causes eliminated, the incidence of eosinophilia in 2363 malignant tumors reviewed at the Jewish Hospital of Brooklyn during the last eight years was 0.54 per cent.

It is obvious that the occurrence of eosinophilia does not depend on the type of tumor involved. It occurs in malignant tumors of both epithelial

and connective tissue origin (29 epithelial, 5 connective tissue). Furthermore, the incidence of eosinophilia in each specific type of tumor corresponds closely to the relative frequency of occurrence of that type. There is no statistical difference in sex incidence, although it has been reported slightly more often in women (19 cases in women, 15 in men).

Thirteen of our 15 cases had metastases which were seen at operation or which became manifest shortly thereafter. A fourteenth case (Case 11) was suspected of having intra-abdominal metastases but this could not be proved. Similar findings were present in the cases previously reported in the literature. Fourteen of the 15 cases, in which details are available, had widespread metastases at the time of operation. The fifteenth case, that of Weiss,⁷ was a patient who had an adenocarcinoma of the stomach in which no metastases were found at the time of subtotal gastrectomy. The eosinophile count dropped to normal post-operatively but shortly returned to its elevated level.* Weiss stated that "Whether this post-operative eosinophilia was due to metastatic growth of the tumor could not be determined."

In two of our cases (12 and 13) pronounced eosinophilia was noted at the time of their first admission. In both these cases, no metastases could be demonstrated then, although they were carefully studied by roentgen-ray and other diagnostic means. The eosinophilia persisted and increased. At subsequent examinations widespread metastases became manifest.

One case, that of cancer of the stomach (number 10), showed an eosinophile count of zero at the time of gastrectomy and no metastases were found at this time. The patient was readmitted 10 months later with an eosinophilia of 13 per cent and metastatic nodules in the liver. Case 11 was similar. The patient had no eosinophilia at the time of radical mastectomy. Five months later, on readmission, she had an eosinophile count of 17 per cent and vague abdominal pains. Intra-abdominal metastases were suspected but could not be proved. A thorough work-up failed to reveal the cause of her complaints. In both of the above cases, other causes of eosinophilia were ruled out.

Case 1 is interesting in that the metastases were so widespread, and the leukemoid reaction and eosinophilia so pronounced that a diagnosis of eosinophilic leukemia was made clinically.

From these facts certain conclusions can be drawn. In 27 of 30 cases of malignant disease with eosinophilia, metastases were present and in two it was suspected but not proved. In only a single case (number 8) was dissemination of the tumor neither suspected nor proved. There was no follow-up of the patient, however, and she might subsequently have developed demonstrable metastases as was the case in numbers 12 and 13. *Eosinophilia when it occurs with malignant tumors, and when other causes can be ruled out, is indicative of dissemination, and consequently significant of a poor prognosis.*

* This occurrence is not uncommon. It was first described by Vosswinkel²⁵ and later by Baradulin²⁸ and Strisower.⁴ Our case 9 illustrates this phenomenon.

Our study fails to throw further light on the pathogenesis of eosinophilia in malignant tumors. Of the 10 cases in which adequate study could be made of the primary tumor, six showed necrosis of tumor tissue (Cases 1, 2, 6, 7, 10 and 13), two showed local tissue eosinophilia (Cases 7 and 9) and three showed osseous metastases (Cases 1, 4 and 12). This would support any of the theories cited in the introduction to this article, but all have weaknesses, and no one explanation has yet been stated which would apply to all cases.

SUMMARY AND CONCLUSIONS

Nineteen cases of pronounced eosinophilia associated with malignant tumors are reviewed from the literature. To these are added 15 cases, making a total of 34. In 90 per cent of all the cases, metastases were present and in an additional 7 per cent they were suspected but not proved. In only one was metastasis neither demonstrable nor suspected. That dissemination may have been present though not clinically manifest is possible, as illustrated by two of our cases. Eosinophilia, when associated with a malignant tumor, with other causes ruled out, is indicative of dissemination of the malignant process.

The prevailing theories as to the pathogenesis of eosinophilia in malignant tumors are discussed. No definite cause has been established as yet.

BIBLIOGRAPHY

1. RHEINBACH: Über das Verhalten der Leukozyten bei malignen Tumoren, *Arch. f. klin. Chir.*, 1893, i, 486.
2. KAPPIS, M.: Hochgradige Eosinophilie des Blutes bei einem malignen Tumor der rechten Lunge, *München. med. Wchnschr.*, 1907, liv, 881.
3. DUNGER: Eine einfache Methode der Zählung der eosinophilen Leukozyten und der praktische Wert dieser Untersuchung, *München. med. Wchnschr.*, 1910, lvii, 672.
4. STRISOWER: Beitrag zur Kasuistic hochgradiger Bluteosinophilie bei einer Karzinomatose und einem Lymphogranulomatose, *Wien. klin. Wchnschr.*, 1913, xxvi, 16.
5. CZÁKI, L.: Case of tumor of colon with high grade eosinophilia, *Wien. klin. Wchnschr.*, 1921, xxxiv, 97.
6. SCHELLONG, F.: Über hochgradige Eosinophilie bei Tumoren, *München. med. Wchnschr.*, 1922, lxix, 553.
7. WEISS, E.: Carcinoma of the stomach with high blood eosinophilia, *Jr. Lab. and Clin. Med.*, 1926, xi, 773.
8. NETCHAEFF, A. A.: Eosinophilia in cancer of the thyroid gland—case, *Vrach. Gaz.*, 1929, xxxiii, 2128.
9. PISA, M.: Eosinophilia in malignant tumor—case, *Minerva Med.*, 1931, i, 152.
10. ROCA DE VIÑALS, R.: Epithelioma of penis with local and circulatory eosinophilia, *An. Hosp. de Santa Cruz y San Pablo*, 1931, v, 168.
11. CHIRAY, M., and BAUDOUIN, E.: De l'éosinophilie sanguine en général, et en particulier au cours de quelques tumeurs malignes, *Presse méd.*, 1931, xxxix, 1869.
12. STERLING, S., and OKUMIEWSKI: Eosinophilia in cancer of the uterine cervix, *Neoplasmes*, 1932, xi, 95.
13. PAVIOT, J., LEVRAT, M., and GUICHARD, A.: Eosinophilia in malignant tumors, discussion in connection with a case of perirenal reticulosarcoma with eosinophilia of blood and tumor, *Ann. d' anat. path.*, 1935, xii, 113.

14. RIOPELLE, J. L.: Eosinophilia during generalization of adenocarcinoma of uncertain origin—case, *Ann. d' anat. path.*, 1930, xiii, 467.
15. SALA, A. M., and STEIN, R. J.: Carcinoma of cervix with blood picture simulating chronic aleukemic eosinophilic leukemia—case, *Am. Jr. Cancer*, 1937, xxix, 125.
16. BASNUENO, J., SUTTAR, R., and PORTELLA, R.: Eosinophilia in malignant ulcerated neoplasm of penis, *Bol. figa contra el cáncer*, 1937, xii, 44.
17. MORGAN, W. G., and BALLINGER, W. M.: Unusual cause for eosinophilic leukocytosis probably due to rapid protein breakdown in hepatic cancer), *Jr. Am. Med. Assoc.*, 1938, cx, 952.
18. LAMANNA, S., and BORGHETTI, U.: Eosinophilia—pathogenesis in tumors, *Tumori*, 1938, xii, 499.
19. SCHEER, G.: High degree of eosinophilia in blood in scirrhus gastric carcinoma—case, *München. med. Wchnschr.*, 1939, lxxxvi, 1939.
20. EHRLICH, P.: Über die specifischen Granulationen des Blutes, *Ztschr. f. klin. Med.*, 1880, i, 553.
21. WINTROBE, M. M.: Clinical hematology, 1942, Lea and Febiger, Philadelphia, Pa.
22. TODD, J. C., and SANFORD, A. H.: Clinical diagnosis by laboratory methods, 10th Edition, 1943, W. B. Saunders, Philadelphia.
23. OSGOOD, E. E.: Textbook of laboratory diagnosis, 3rd edition, 1944, Blakiston Co., Philadelphia.
24. KIRK, R. C.: Causes of eosinophilia, *Internat. Clin.*, 1942, i, 219.
25. VOSSWINKEL: Über das Vorkommen von eosinophilen Zellen und Myelocyten im menschlichen Blute bei Erkrankungen der inneren weiblichen Geschlechtsorgane, *Monatschr. f. Geburtsh. u. Gynäk.*, 1898, vii, 413.
26. DOWNEY, H.: Handbook of hematology, 1938, Paul B. Hoeber, Inc., New York.
27. COLLINS, J., and KAPLAN, D.: Studies of the blood in diseases commonly called nervous diseases, *Am. Jr. Med. Sci.*, 1911, cxlii, 702.
28. BARADULIN, G. T.: Über Blutveränderungen bei malignen Neubildungen, *Folia haematol.*, 1910, ix, 407.
29. WHARTON, J.: *Philos. Trans.*, 1846.
30. RINDFLEISCH: Experimental Studien über die Histologie des Blutes, 1863, Leipzig.

THERAPEUTIC TRIAL OF PENICILLIN IN TETANUS*

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THE clinical usefulness of penicillin has been expanded through laboratory determinations of its antibacterial power in vitro and also through clinical trial in a great variety of infections in which there was frequently little reason to anticipate success. In the case of tetanus, studies in the laboratory have indicated that *Clostridium tetani* is affected by penicillin in fairly high dilutions. Abraham and his associates¹ report complete inhibition of *Clostridium tetani* grown in Lemco broth at a dilution of 1,000,000. This figure is the same as that given for *Staphylococcus aureus* by the same authors. Organisms grown in beef broth were inhibited at a dilution of only 100,000. Hobby, Meyer and Chafee² did not list *Cl. tetani* among the organisms susceptible to penicillin, but Herrell, Nichols and Heilman³ did. Robinson⁴ found growth of the organism completely inhibited in dilutions of 1:200,000 and partially in 1:400,000. However, there are no reports known to the writer of critical evaluation of the drug in human cases. Although it has been used in a few isolated instances, the patients have also reportedly received tetanus antitoxin and other adjuncts of therapy.⁵ It seemed important, therefore, to take advantage of an opportunity to study tetanus among the civilian casualties in the Okinawan campaign and to determine, if possible, whether penicillin had a place in the treatment of the disease. To this end Major (now Lt. Col.) Harvey G. Taylor arranged for a supply of penicillin from Army sources which was used in the following study.

Although the number of cases of tetanus treated in Military Government dispensaries and hospitals is not accurately recorded, it is estimated that over 300 were seen. When this investigation was undertaken early in July 1945, after the peak load of battle casualties had passed, 46 with tetanus were found in one of the large hospitals (G-6, 59) which had a patient load of over 1200 at that time. Unfortunately, the opportunity for clear-cut research was somewhat hampered by the type of cases then available. The most satisfactory case, assuming that the late symptoms of tetanus are due principally to fixed toxin, is the acute early one in which an antibacterial effect might be clearly recognized. Prompt arrest of development of symptoms followed by clinical improvement in such a patient would probably indicate susceptibility of *Cl. tetani* to penicillin in vivo. However, those with early acute tetanus generally failed to survive for transportation to the hospitals situated in the northern civilian areas or had already had the disease modified by treatment with antitoxin. From the group of patients available, those were selected

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TABLE I

Case Number	Age	Sex	Interval:		Nature of Injury	Date of Injury	Date of Tetanus	Grade of Trismus	Local Tetanus	General Tetanus	History of Convulsions	Observed Convulsions
			Injury-Tetanus	Tet.-Penicillin								
			Days									
1611	12	M	8	7	Mult. shrap.—head, l. arm	6-23	7-1	+++	—	+	—	—
962	27	F	17	4	Amp.—rt. mid-arm	6-17?	7-4	++++	—	++	—	—
1098	39	F	12	4	Shrap.—l. arm; burns—leg	6-22	7-4	++++	Rt. leg	+	—	—
1679	20	F	5	6	Rt. leg amp.—mult. shrap.	6-28	7-3	++++	Neck ++	++	—	++
1114	40	F	15	11	GSW—rt. knee	6-12	6-27	++++	Rt. lower ext.	++	—	—
728	49	F	14	6	Shrap.—ankle, buttocks	6-18	7-2?	+++	—	++	—	—
1265	22	F	12	4	GSW—l. thigh, rt. ankle	6-22	7-4	++	L. thigh	—	—	—
942	39	F	?	?	Scalp avulsion	6-22	?	++++	—	+++	—	—
2040	70	F	25	5	Shrap.—l. scapula, rt. leg	6-12	7-7	++++	—	++	—	—
990	21	F	20	10	Shrap.—lumbar, l. arm	6-8	6-28	+++	—	+++	—	—
*1998	17	M	4	4	GSW—l. buttock	7-1	7-5	+++	—	++++	+	++
1184	54	F	16	4	GSW—l. chest	6-18	7-4	++++	L. arm	+++	—	—
1431	27	F	42 #	3	Shrap.—rt. low ext.; partial amp.—rt. foot	5-23	7-5	+++	—	++	—	—
1526	47	M	22	6	Shrap.—l. eye and face	6-8	6-30	++++	—	+++	—	+
2093	22	F	?	?	Shrap.—l. thigh; GSW—leg	6-13	?	—	L. lower ext.	—	—	—

who had most recently developed symptoms and whose tetanus was not only severe but either untreated or unaffected by antitoxin. In most instances there were major infected wounds, and the difficulty of discriminating between death due to wounds and death due to tetanus was foreseen. However, the effect of penicillin in other diseases has often been dramatic, and the patients selected offered every opportunity for demonstrating a striking therapeutic effect.

The accompanying tables 1, 2, and 3 present in summary form the clinical data of 15 cases treated with penicillin, four treated with antitoxin of known amount, and 27 random cases, some of whose records failed to disclose the

TABLE II

1605	21	F	10	—	Shrap.—rt. thigh	6-18	6-28	++	—	—	—	—
1541	39	F	3	—	Amp.—rt. arm	6-17	6-20	+	—	+	—	—
881	20	F	10	—	Shrap.—rt. buttock	6-17	6-27	+	Rt. and l. lower ext.	+	—	—
*1997	19	M	10	—	GSW—rt. knee and l. thigh	6-24	7-4	++++	Rt. hamstring	++	—	+

* See case reports.

TABLE I.—*Continued*

Date	Tetanus Antitoxin Administered	Date	Tetanus Antitoxin Previously Administered	Date	Penicillin Administered	Result	Comment
—	None	—	None	7-8	460,000 U—120 hrs.	Recov.	Poor selection for trial
—	None	—	None	7-8	280,000 U—72 hrs.	Died 7-11	Febrile; necropsy neg.
—	None	—	None	7-8	500,000 U—116 hrs.	Recov.	Slow imp. after 7-16
7-15	80,000 U	—	None	7-8	500,000 U—116 hrs.	Died 7-24	Febrile; no necropsy
—	None	7-4 & 5	200,000 U	7-8	500,000 U—116 hrs.	Improved	Relaxed 7-15; free 7-26
—	None	6-30	20,000 U	7-8	500,000 U—116 hrs.	Recov.	Grad. imp. after 1st wk.
—	None	—	None	7-8	500,000 U—116 hrs.	Recov.	Grad. imp. after 1st wk.
7-15	6,000 U	6-25	40,000 U	7-8	500,000 U—116 hrs.	Died	No imp. 1st wk; mult. abscesses
—	None	—	None	7-11	710,000 U—87 hrs.	Recov.	Grad. imp.
—	None	—	None	7-8	500,000 U—116 hrs.	Recov.	Grad. imp. Infect. imp.
7-14	100,000 U I-V	—	None	7-9	650,000 U—124 hrs.	Recov.	No imp. with penicillin
—	None	—	None	7-8	500,000 U—116 hrs.	Died 8-1	Progressive tetanus
—	None	6-26	1500 U	7-8	500,000 U—116 hrs.	Improved	Grad. imp.
—	None	—	None	7-8	500,000 U—116 hrs.	Died 7-23	Persistent tetanus
7-15	20,000 U I-M	—	None	7-13	150,000 U—Locally	Improved	No reaction to trt.

exact dosage or date of administration of antitoxin. The latter group (table 3) was considered satisfactory to serve as a rough control. The penicillin-treated group and the four antitoxin-treated patients were kept under observation with the same general ward management. The others were not under direct supervision but were followed in other wards. Among the 15 patients who were given penicillin, there were three who had previously been injected with therapeutic amounts of antitoxin, and one had received a single prophylactic dose. These four were included in the group for clinical trial of penicillin since they had severe tetanus and had apparently failed to benefit from antitoxin.

TABLE II.—*Continued*

7-7	1,500 U I-M	?	113,500 U			Recov.	Progressive imp.
7-7	3,000 U I-M	?	?			Recov.	Progressive imp.
—	None	7-4	100,000 U			Recov.	Progressive imp.
7-9	100,000 U I-V	—	None			Recov.	Prompt response to trt.

TABLE III

Case Number	Age	Sex	Interval: Injury-Tetanus	Nature of Injury	Date of Injury	Date of Tetanus	Grade of Trismus	Local Tetanus	General Tetanus	History of Convulsions	Observed Convulsions
			Days								
2057	27	F	14	Comp. fract.—rt. femur	6-21	7-5	++	—	±	—	—
1561	54	F	30?	Shrap.—head, neck, chest	6-5?	7-1?	+++	—	+	—	—
1651	34	F	7	Shrap.—rt. foot, leg; l. shoulder	6-22	6-30	++++	—	+	—	—
1652	16	F	.5	Shrap.—rt. knee, l. leg	6-17	6-22	+++	Rt. foot	++	—	—
1654	54	F	10	Shrap.—rt. forearm; temple	6-17	6-27	+++	—	+	—	—
1649	24	F	17	Shrap.—rt. thigh	6-12	6-30	+++	—	+	—	—
1653	20	F	13	Fractured—l. arm	6-11	6-24	+++	Slight	+	—	—
1647	36	F	17+	Shrap.—head	6-7+	6-24	++++	—	+	—	—
1739	16	M	21	Comp. fract.—l. leg	6-15	7-13	++++	—	+	—	—
1627	66	M	10	Shrap.—l. leg, rt. arm	6-8	6-18	++++	Rt. forearm	+	—	—
1624	25	F	14	GSW—l. leg	6-8	6-22	++	—	—	—	—
1638	26	F	15	Shrap.—l. arm and leg	6-8	6-23	+++	—	++	—	—
1625	61	M	6	Shrap.—l. hand	6-18	6-24	+	—	+	—	—
1641	22	F	10	Shrap.—l. buttock; temple	6-18	6-28	+++	L. thigh	++	—	—
1640	41	F	10	Shrap.—rt. hand	6-18	6-28	+++	—	—	—	—
1170	18	M	4	Shrap.—rt. and l. feet	6-24	6-28	++++	Rt. low. ext.	+	+	+
1644	20	F	24	Shrap.—rt. shoulder	6-8	7-2	+++	—	+	—	—
1645	29	F	9	Amp. rt. arm	6-16	6-25	++++	—	+	—	—
1646	26	F	16	Shrap.—rt. hip	6-8	6-24	+	—	±	—	—
1639	39	F	15	Shrap.—rt. buttock	6-8	6-23	++	—	—	—	—
1636	28	F	15	Shrap.—rt. arm	6-13	6-28	++	—	+	—	—
795	17	M	7	Comp. fract.—l. leg	6-18	6-25	++	—	++	—	—
1635	24	F	10	Shrap.—both arms; rt. amp.	6-18	6-28	++	—	—	—	—
1667	30	F	12	Shrap.—back	6-18	6-30	+++	—	+	—	—
506	11	M	?	Comp. fract.—l. leg; shrap.	?	?	++++	Moribund			
765	24	F	?	Shrap.—l. leg, rt. chest	?	?	+	—	++	—	—
1831	20	F	4	Comp. fract.—rt. arm; shrap.—rt. neck	6-28	7-2	++	—	Toxic	—	—

PENICILLIN TREATED GROUP

Three males and 12 females of ages varying from 12 to 54 years, all of them showing signs of severe tetanus, were selected for trial of penicillin. Nine were suffering from the effects of multiple or severe shrapnel wounds, four from gun-shot wounds, and one had the right arm amputated at the mid-humerus for an undetermined type of injury. All had open and infected

TABLE III.—Continued

Date	Tetanus Antitoxin Administered	Date	Tetanus Antitoxin Previously Administered	Result	Comment
?	1500 U on admission	—	None	Improved	Sl. trismus persists 7-13
7/4-7	33,000 U	—	None	Improved	Up and about 7-13
7-6 7-12	4,500 U 3,000 U daily, 4 days	?	2 inj. daily, 5 days	Recov.	Discharged well 7-23
7-12	3,000 U daily, 4 days	?	7 inj.; 1500 U on 7-6	Recov.	Up and about 7-26
7-12	3,000 U daily, 4 days	?	2 inj. daily, 3 days	Recov.	Discharged well 7-23
7-6	3,000 U I-V; 1500 U I-M	?	2 inj. daily, 5 days	Recov.	Condition good 7-13
7-6 7-12	3,000 U I-V; 1500 U I-M 3,000 U daily, 4 days	?	7 inj. in 5 days	Recov.	Up and about 7-26
7-12	3,000 U I-M	?	3 inj. in 2 days	Improved	Tetanus absent 7-26
7-14	80,000 U	—	None	Died 7-15	Died 3 days post-operative,
—	None	?	2 inj. daily, 7 days	Recov.	Discharged well 7-15
—	None	?	8 injections	Recov.	Tetanus absent 7-26
—	None	7-3	1 inj. Dose?	Improved	Trismus and stiff neck persist 7-26
—	None	?	4 inj. in 4 days	Recov.	Tetanus signs absent 7-26
—	None	?	5 inj. Dose?	Improved	Moderate trismus persists
—	None	?	3 inj. in 2 days	Recov.	Discharged well 7-26
—	None	?	5 inj. in 5 days	Recov.	Tetanus signs minimal 7-26
—	None	?	1 I-V inj.	Improved	Tetanus subsiding 7-26
—	None	?	7 injections	Recov.	Discharged well 7-19
—	None	?	8 injections	Recov.	Minimal tetanus 7-26
6-28	1 inj. I-V, dose?			Recov.	Discharged well
—	None	?	2 inj. daily, 3 days	Recov.	Improved 7-13, well 7-26
—	None	?	1500 U prophylactic	Improved	
—	None	?	7 injections	Recov.	Tetanus signs absent 7-26
—	None	?	5 injections	Recov.	Tetanus signs absent 7-26
—	None		No history	Died	Death from wound infection
6-22	1500 U	—	None	Died 7-11	Wounds chief cause of death
—	None	?	3 injections	Worse	Tetanus more marked 7-25

wounds, some of which were severe: avulsion of most of the anterior scalp (No. 942); loss of the left eye, most of the orbit and maxilla (No. 1526). One patient, a 12 year old male, proved to be a poor selection for this group since he began to improve rapidly before penicillin was started and would undoubtedly have recovered without treatment. Patient No. 2093 was the only one to receive only local injections of penicillin into the region of her wounds. In all other cases the intramuscular route was used.

Fourteen patients received 20,000 units of penicillin * intramuscularly every four hours (except during the interval 2200 to 0600, when only native nurses' aides were on duty in the wards), a total of 100,000 units in 24 hours, for approximately five days. In some instances larger doses were given more frequently toward the end of the course.

Seven patients recovered, five of whom had not received antitoxin at any time, one who received 20,000 units on June 30 and another (No. 1998) who was given 100,000 units intravenously on July 14 after having failed to improve under penicillin therapy. One patient, as noted above, had already improved considerably before penicillin was started (No. 1611). The other four who received no antitoxin but recovered (Nos. 1098, 1265, 2040, 990) showed gradual abatement of symptoms during the second week. There was no sharp alteration of clinical course during the period of treatment or within the first three or four days following injections of penicillin. In most instances the wounds became cleaner and in this respect treatment was undoubtedly beneficial and indicated. However, the course of tetanus seemed no different from that in the patients who had received only prophylactic antitoxin, and all the patients who recovered slowly seemed to have weathered the disease without much evidence of influence by treatment. The final patient of this group (No. 1998) who was given antitoxin after failure of penicillin will be discussed in detail in a comparison with a similar case treated immediately with antitoxin.

Five deaths occurred: Nos. 962, 1679, 942, 1184, 1526..

Case No. 962 was the only one examined post mortem. This patient had pronounced trismus, neck and back rigidity, and during the course of her illness developed dysphagia and later diarrhea. Her course was febrile and remained so although the amputation stump of the right humerus which exuded pus freely on July 8 was clean at the time of death. Necropsy showed no visceral lesion to account for the fever and was negative except for a small area of phlebitis of the deep pelvic veins and ascariasis. (Autopsy was performed by Lt. Comdr. Harold Fink, MC, USNR.) In the absence of other evident cause, this death may be attributed to tetanus, and it is significant that although tetanic symptoms were of only four days' duration there was no apparent abatement with penicillin therapy.

Patient No. 1679, a 20 year old female with multiple shrapnel wounds and amputation of the right leg, exhibited gradually more severe tetanus from onset to death. By the end of a week's observation it was obvious that penicillin had been ineffectual, and tetanus antitoxin in a dose of 80,000 units was administered intravenously. The clinical course was not significantly altered by this measure, resorted to on the twelfth day of tetanus, and the patient slowly deteriorated to die on the twenty-first day of the disease. In this instance the temperature ranged from 99.6° to 100.6° F. (rectal) until the twelfth day of tetanus at which time it rose to 104.4° F. and remained elevated for the remainder of the illness.

No. 942 was a debilitated 39 year old female whose scalp had been partially avulsed by a stone contusion. On July 8 the remaining parieto-occipital scalp was loose and free pus could be readily expressed. Following penicillin the infection cleared suf-

* The penicillin used was of the following manufactures and lot numbers: CSC-Commercial Solvents, Lot No. 44121801, Expiration date Dec. 1945. Squibb, Lot No. 3351-1, Expiration date Dec. 28, 1945. The sodium salt of penicillin was used throughout.

ficiently to permit surgical intervention. On July 13 Lt. Comdr. D. J. Kweder, MC, USNR, made multiple drill holes in the outer table of the skull with the object of permitting granulations to protrude from the diploe to make a base for subsequent skin grafting. Even while receiving penicillin, however, abscesses developed at the left elbow and later the left buttock. The latter lesion failed to heal after repeated incisions for drainage. There was no growth of granulations from the perforations of the skull. The patient gradually weakened. By July 26 she had less trismus than was present at the outset, and in the writer's opinion she would have recovered from tetanus had she not suffered the complicating infections. Death on August 9 was considered due principally to pyogenic infection. A culture from the pus of this lesion was reported to have shown "young forms (Gram positive rods) and suspicious tack-head types" of tetanus organisms on liquid thioglycollate medium.

Patient No. 1184, a 54 year old female, had a superficial wound of the left chest wall and showed extreme localized tetanus of the left arm and left side of the neck. The head was flexed and rotated sharply to the left, the upper back muscles were rigid, and motion of the chest was restricted. The patient was mentally alert throughout her illness and required sedatives and analgesics frequently. After a week tetanic spasm spread to involve the lower extremities, and later the abdomen became board-like and the trunk extremely rigid. The course of her illness was not influenced by penicillin. Death occurred on August 1, the twenty-seventh day of the disease.

When he was selected for therapeutic trial with penicillin patient No. 1526, a 48 year old male, seemed to have advanced tetanus and a destructive wound of the face. Later he developed pulmonary symptoms which complicated his illness and probably caused his death. As a result of shrapnel he lost the left eye, most of the orbit and part of the maxilla. The wound was an open, granulating lesion with moderate secondary infection. Following penicillin treatment the granulations became cleaner and healthier appearing. However, trismus and stiffness of the back were followed by spasm of thoracic muscles and impairment of respiratory motion. Orthopnea developed on July 15 and persisted. The only finding on chest examination was impairment of resonance. Death occurred on July 23, on the twenty-fourth day of tetanus. Evaluation of the rôle of pulmonary disease as a cause of death would have been easier had necropsy been performed, but on the basis of the clinical findings there can be little doubt that tetanus was an important contributory cause.

Local injection of penicillin was given in one instance.

The administration of penicillin directly into the region of her wounds had no beneficial effect upon the localized tetanus in case No. 2093. Two injections, one of 60,000 units around a wound of the leg and 90,000 units into and around a wound of the thigh, were given on July 13. There was no improvement after 48 hours, and an injection of 20,000 units of antitoxin was given intramuscularly on July 15. Spasm of the leg muscles began to subside on July 19 and by July 26 only equinus contraction of the foot remained.

In summary, the 14 patients treated by intramuscular injection of approximately 100,000 units of penicillin daily for about five days failed to show any definite evidence of alteration of the clinical course of the disease which seemed attributable to therapy. Those who recovered exhibited no sharp amelioration of symptoms but slowly improved in the manner of other patients who received minimal doses of antitoxin. (See section on the rough control group of 27 patients.) Since the over-all mortality from tetanus among the civilian casualties is not known, no comparison can be

made on a statistical basis, but it was common knowledge that recovery not infrequently occurred without specific therapy.

COMPARISON OF PENICILLIN AND ANTITOXIN TREATMENT IN SIMILAR CASES

Perhaps the best opportunity for therapeutic evaluation occurred when, on July 9, two young male patients, Nos. 1997 and 1998, were admitted to the hospital. Both of these patients came down with acute tetanic symptoms within the preceding five days; both had wounds which were relatively simple and clean, and both exhibited about the same severity of symptoms: extreme trismus, generalized rigidity and convulsive seizures at frequent intervals—especially when subjected to sharp noises or physical shocks. The patient selected for treatment with penicillin most nearly satisfied the criteria considered desirable when the plans for this study were made: he had a simple and fairly clean wound; tetanus developed four days after injury and was acute and severe. The one chosen for antitoxin treatment had a longer incubation period (10 days as opposed to four) and the onset of tetanus was one day earlier. These cases are reported in detail.

Case No. 1998. An Okinawan farmer, age 17, male, was admitted from a Military Government dispensary on July 8 with a history of gunshot wound of the left buttock on July 1. Trismus developed on July 4 and rigidity of the muscles of the neck, back, abdomen and extremities became progressively worse from that time. Frequent extensor convulsive episodes associated with acute trismus occurred during observation and could be precipitated by touching the patient's cot or by making a loud noise. The only voluntary motions fairly easily accomplished were flexion and extension of the upper extremities. Otherwise the patient was in complete and continuous extensor rigidity. Attempted motion was extremely painful.

Penicillin was given intramuscularly in 20,000 unit doses every 'four hours (except at 0200; five doses in 24 hours) for 25 doses, then in 50,000 unit doses every three hours for an additional three injections. The total amount of penicillin administered was 650,000 units.

During the period of treatment it was necessary to resort to the use of barbiturates frequently. Even during the height of sedative action contractures could be readily precipitated. The patient's status showed very little alteration during the first week of observation and treatment. He did not become worse, although exhaustion became more pronounced, yet he showed no sign of remission. The degree of tetanus was remarkably constant, and there were no changes which could reasonably be ascribed to a therapeutic agent. Finally, on July 14, having concluded that penicillin had not been of benefit, a culture was made from the wound and later 100,000 units of tetanus antitoxin were given intravenously at 1830.

There was no change the following day, but within four days trismus subsided and muscular spasms ceased. On July 26 knee flexion of 15 to 20 degrees was first possible. The abdomen was less rigid and the neck was free. This was the last date of observation, but the patient was later reported to have made a complete recovery.

Unfortunately, facilities were not available for full identification of the organism cultured from the wound at the end of penicillin treatment, but an Army Station Hospital laboratory reported as follows on the culture taken July 14: "Few streptococci seen; occasional Gram-positive rod (young form of tetanus bacillus); no 'tack-head' forms seen."

Case No. 1997. An Okinawan male, age 19, admitted on July 8 with a history of bullet wounds of the upper left thigh and the right knee region. The injuries were sustained on June 24 and trismus was first manifested on July 4. By July 7 trismus was extreme, and generalized tetanic spasm had supervened. Acute spasms of the face and extremities occurred fairly frequently and could be precipitated by external stimuli. The degree of tetanus was not quite so severe but approached that shown by patient No. 1998.

At 1315 on July 8 the patient was given 100,000 units* of tetanus antitoxin intravenously. A brief period of rigor occurred at 1430, but there were no other reactions to the serum. Within four hours of the administration of antitoxin there was evident muscular relaxation. Local tetanus which had been pronounced in the right leg muscles diminished promptly, although it recurred on the third day. On the day following antitoxin injection there seemed to be some exacerbation of muscle tension, but following the second day there was progressive improvement, and convulsive phenomena did not occur after treatment was given. By July 26 the patient had almost fully recovered and was able to be up and about.

ANTITOXIN TREATED GROUP

The four patients selected for comparative observation with the penicillin treated group (see table 2) included case No. 1997 which is discussed above. Two others were selected because they had received large doses of antitoxin several days (nine and six respectively in cases No. 1605 and 881) after the onset of tetanus, and one (No. 1541) because she was apparently making a good recovery from severe tetanus following only 3000 units of antitoxin.

On July 8 there was fairly marked trismus and slight neck rigidity noted in patient No. 1605, a 21 year old female with shrapnel injury of the right thigh. She had been given 113,500 units of antitoxin at another hospital before admission and an additional 1500 units on July 7. There was noticeable improvement daily, and trismus as well as nuchal rigidity was no longer present on July 12. The shrapnel wound granulated well and healing progressed normally. Patient No. 1541, a 39 year old female, was admitted with the right arm amputated and with a history of tetanus of 17 days' duration. She had moderate neck rigidity and slight trismus, showed progressive improvement and was free of tetanus on July 15. The third patient, No. 881, a 20 year old female with a severe shrapnel wound of the right buttock, had moderate local tetanus of both lower extremities and slight neck rigidity and trismus. A large dose of antitoxin was given seven days after the onset of trismus, and improvement was progressive and satisfactory. On July 12 she was able to be up and about and by July 15 there was little evidence of tetanus.

OBSERVATION OF 27 CASES TREATED ON GENERAL SERVICE

Although this group of patients does not give a complete picture of tetanus among civilian casualties, it serves as a sort of background for the observations reported above. Tetanus of all degrees of severity occurred in patients with all manner of injuries and burns. The fulminating cases did not survive more than a few days, and none† of these was seen at the

* All antitoxin dosages given are in American units.

† Case No. 1739 may be an exception, but it was impossible to obtain reliable information because of his poor condition when first seen.

time of this study. Many of the milder cases recovered without antitoxin therapy. The dosage of antitoxin given the patients in this group depended upon many factors: the amount available at the hospital where treatment was first rendered, the number of patients under the care of each medical officer, and the organizational status of the hospital. At times only the most cursory type of medical attention could be given, especially in hospitals which were activated with scant notice or inactivated at the height of the emergency on various grounds of military necessity, or for other reasons.

As will be seen in table 3, all but one of the 27 patients are known to have had antitoxin. The dosages and dates of administration were frequently doubtful since most of the patients were transferred from other hospitals without records. Sixteen of these patients, most of whom had received inadequate antitoxin according to current standards, made complete recoveries, and seven others improved sufficiently to indicate probable ultimate recovery. Only three deaths occurred in this group, but one patient who became progressively worse while under observation probably terminated fatally. None of the three fatal cases came to necropsy.

Patient No. 1739, a 16 year old male with badly compounded fractures of the left tibia and fibula, was operated upon the day before he was first seen by the writer. He was found to be extremely ill and to have marked trismus and neck rigidity. Ward attendants were of the opinion that tetanus developed acutely following operation. Tetanus antitoxin in a single dose of 80,000 units was given on the second postoperative day, and the patient died the following day.

Patient No. 506, an 11 year old male with shrapnel wounds of the right shoulder and a compound fracture of the left leg, was moribund when first examined and no history was obtainable. There was no record of antitoxin therapy. The boy lay on his cot saying the word "maggots" over and over and many of the creatures of which he had learned the name were seen crawling out of the opening of the cast. Death occurred three days after the first examination, probably from wound infection and anemia. Tetanus was slight in degree.

The only other patient of this group who died, No. 765, a 24 year old female, had only slight evidence of tetanus and showed marked toxicity from her wounds: a shrapnel injury of the left leg and a large wound of the right chest. She was able to give little reliable information. Death occurred on the fifth day of observation and was considered the result of wounds and infection.

The last patient of this group, No. 1831, a 20 year old female with a compound fracture of the right arm and a wound of the right side of the neck, exhibited increasingly severe tetanus throughout the period of observation. There was marked stiffness of the neck and complete trismus, as well as pallor and evident toxicity. When last seen on July 26 a fatal outcome was anticipated.

DISCUSSION

The symptoms of tetanus are believed to be due to a diffusible exotoxin which reaches the motor neurons and neuromuscular end organs through the circulation.^{6, 7, 8} The circulating toxin exerts its effect upon spinal and medullary motor nerve cells and eventually some, it is thought, becomes irreversibly fixed to the cells. It is obvious, therefore, that a purely anti-

bacterial agent cannot be expected to produce immediate mitigation of clinical symptoms. Antitoxin, which has a direct effect upon the symptom-producing agent, would be expected and actually does frequently produce such amelioration, although its effect may be minimal in late cases. Recovery from the bacterial infection cannot, however, be reasonably ascribed to antitoxin and must be due to natural mechanisms for overcoming the *Clostridium*. Conceivably, therefore, an effective antibacterial agent could influence both the clinical course and the rate of recovery from tetanus by inhibiting the growth and toxin production of the organisms. The manifestations of those influenced would, of course, be most marked in an early infection but, conceivably, mortality reduction might be manifested in a large group of patients with tetanus of varied duration.

The difficulty of selection of early, uncomplicated cases of tetanus at the time of this investigation has already been stated. However, the opportunity to compare the effect of penicillin with that of antitoxin in cases No. 1998 and 1997 was a fortunate one, and the group of cases selected provided a test of the ability of penicillin to alter the course or prevent death in subacute but severe tetanus.*

It is possible that the failure of penicillin in this series was due to inadequate dosage or failure to maintain a blood level throughout the 24 hours. The lack of facilities for determination of blood level and for in vitro testing of bactericidal action was a serious hindrance to the study. In the future consideration should be given to possible effects of large booster doses such as have been used in subacute bacterial endocarditis.⁹ Further controlled investigation, including trial with various fractions not always present in

* An interesting experiment which is to be submitted for publication by 1st Lt. Dwight L. Lichty, VC, AUS, of the 145th Veterinary Food Inspection Department, was brought to the writer's attention by personal communication. Lt. Lichty had the opportunity to treat a horse afflicted with tetanus on the first day of development of symptoms. The animal was seen at the Taira Military Government corral because of a puncture wound which occurred on September 19, 1945. The horse was small, weighing only 600 lb., but was in generally good condition. The puncture wound was located just below the stifle, right anterior. Ten days after injury, on September 29, 1945 tetanus was manifested by a saw-horse stance, extended neck, rigidity of the legs and early trismus. Loud noise produced slight muscular spasm and complete contraction of nictitating membranes. The horse was placed in a sling. Nutrition was maintained by tube feeding as well as voluntary eating during periods of relaxation. Barbiturates and chloral were used in maximum doses to effect sedation and muscular relaxation. Tetanus antitoxin was not employed.

Penicillin in doses of 100,000 units each was administered every three hours for 90 hours. (The recommended dose for an average size horse in treatment of susceptible infections is 50,000 units every three hours). Of the 30 original doses, three were given intrathecally, the others intramuscularly. After the ninetieth hour 50,000 units were injected intramuscularly every three hours through the one hundred and thirty-eighth hour. One million units was given each 27 hours during the first 30 injections. The total penicillin administered was 4,100,000 units.

During the course of this treatment the animal showed persistent and complete trismus and failed to respond to therapy. It died on the morning of the eighth day, approximately 170 hours after the onset of therapy.

This interesting clinical trial is important because the amount of penicillin administered was twice the recommended therapeutic dosage. It was possible to give injections every three hours and thus presumably to maintain a satisfactory blood level. Treatment was instituted at the earliest possible moment, and no therapy other than sedatives was given.

commercial penicillin, is warranted before arriving at final conclusions, especially in view of the laboratory reports of in vitro inhibition of *Clostridium tetani* already referred to above.

SUMMARY AND CONCLUSIONS

1. Fifteen cases of tetanus of three to 11 days' duration were treated by intramuscular injection of penicillin in doses of 20,000 units every four hours with the exception of the interval 2200 to 0600. Most of the patients received a total of 500,000 units or more. One patient was given 150,000 units in injections about her wounds.

(a) Of this group seven patients recovered, three (including the patient injected locally) improved, and five died. In none of the cases treated was there observable alteration of the course of tetanus which seemed attributable to the use of penicillin. Wound infections were generally benefited, and the indication for use of the drug in complicating infection is clear. However, there was no tendency toward reduction of mortality in severe tetanus and no improvement in cases which had failed to respond to antitoxin. Recovery and improvement were gradual in the cases which survived, and the clinical course was comparable to that in other cases which recovered after only prophylactic doses of antitoxin or without any treatment whatever.

2. Four patients who had received or who were given known amounts of antitoxin were observed under conditions identical with those of the penicillin group. These patients showed a striking clinical change after administration of antitoxin. One of the four was comparable in many respects to a patient treated with penicillin, and the favorable response to antitoxin was in sharp contrast to the failure of penicillin to affect the course of the disease.

3. Twenty-seven patients on general service who had received undetermined amounts of antitoxin were observed during the 18 day period of investigation. Of these patients, most of whom had been given small and presumably inadequate amounts of antitoxin, 16 made complete recoveries, seven others improved and three died. One patient declined progressively and probably terminated fatally.

4. The relatively high mortality in the first group was attributable largely to the selection of patients with severe tetanus in order to test the possible efficacy of penicillin. It would obviously have been difficult to evaluate a drug in a series in which recovery would have been anticipated under any type of therapy.

5. On the basis of this study there are no indications that commercial penicillin is an effective agent in the treatment of tetanus. In vitro evidences of antibacterial action are not supported by clinical indications of a similar effect in vivo. The possibility is mentioned that other penicillin fractions or larger doses may be effective.

BIBLIOGRAPHY

1. ABRAHAM, E. P., CHAIN, E., FLETCHER, C. M., GARDNER, A. D., HEATLEY, N. C., JENNINGS, M. A., and FLOREY, W. H.: Further observations on penicillin, *Lancet*, 1941, ii, 177-189.
2. HOBBS, G. L., MEYER, K., and CHAFEE, E.: Activity of penicillin in vitro, *Proc. Soc. Exper. Biol. and Med.*, 1942, 1, 277-280.
3. HERRELL, W. E., NICHOLS, D. R., and HELLMAN, D. H.: Penicillin: its usefulness, limitations, diffusion and detection, with analysis of 150 cases in which it was employed, *Jr. Am. Med. Assoc.*, 1944, cxxv, 1003-1011.
4. ROBINSON, H. J.: Toxicity and efficacy of penicillin, *Jr. Pharmacol. and Exper. Therap.*, 1943, lxxvii, 70-79.
5. BUXTON, R., and KURMAN, R.: Tetanus: A report of two cases treated with penicillin, *Jr. Am. Med. Assoc.*, 1945, cxxvii, 26.
6. ABEL, J. J.: On poisons and disease and some experiments with the toxin of the *Bacillus tetani*, *Science*, 1934, lxxix, 121.
7. ABEL, J. J., and CHALIAN, W.: Researches on tetanus, IV, *Bull. Johns Hopkins Hosp.*, 1935, lvii, 343; and Researches on tetanus, VIII, *ibid.*, 1938, lxii, 610.
8. HARVEY, A. M.: The peripheral action of tetanus toxin, *Jr. Physiol.*, 1939, xcvi, 348.
9. Treatment of subacute bacterial endocarditis caused by gamma Streptococci, *BuMed News Letter (U. S. Navy)*, 1945, vi, 6.

THE PREPONDERANCE OF RIGHT HYDROTHORAX IN CONGESTIVE HEART FAILURE *

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ALTHOUGH there has been a strong clinical impression that right hydrothorax is more common than left hydrothorax when gross congestive heart failure occurs, recently this point of view has been questioned. In a survey by Bedford and Lovibond,¹ these authors were led to the conclusion that although right hydrothorax was more common in cases showing mitral stenosis, combined right and left heart failure and auricular fibrillation, the occurrence of left hydrothorax was favored by hypertension, left heart failure and normal rhythm. Owing to the strong impression we have had that right hydrothorax was much more common in congestive heart failure, regardless of the underlying cause, the following study was made to determine the actual facts. Consecutive cases of congestive heart failure showing hydrothorax were selected, after eliminating those presenting extraneous factors, such as pleurisy with effusion, active rheumatic fever, significant nephritis, blood dyscrasias, neoplasm, hepatic disease, etc. The purpose of this was to include for consideration only those suffering from clear-cut cardiovascular disease with congestive failure.

The first method of approach was to review 75 clinical cases of congestive heart failure that required thoracentesis. In each case the side of the chest tapped was the only one in which fluid appeared to be present or was the one that seemed to show the larger degree of hydrothorax, where some disproportion in the two sides existed. This decision was made by the ordinary methods of bedside examination with or without the aid of roentgen-ray. The second analysis consisted of comparing the roentgen-ray findings in 52 consecutive cases of congestive heart failure with hydrothorax. In no instance had thoracentesis been performed in this group, and the relative degree of hydrothorax on the two sides was estimated by the roentgenologist. The basis of the third study consisted in determining the amount of fluid in the two pleural cavities in 110 cases of congestive heart failure that came to postmortem examination. The above three analyses ought to serve as controls for each other and should give convincing evidence if they all agree in their conclusions.

Of the 75 cases of hydrothorax requiring thoracentesis (table 1), 35 had rheumatic heart disease, 22 had a significant degree of coronary sclerosis and 18 had hypertensive heart disease. Owing to the tendency for hydrothorax to recur following thoracentesis, no more than two chest taps from

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TABLE I
Hydrothorax in Congestive Heart Failure, Thoracentesis

Heart disease		Rheumatic	Coronary	Hypertensive	Total
Site of hydrothorax	R*	28	16	11	55
	L	3	1	4	8
	B	4	5	3	12
Total cases		35	22	18	75
Site with auricular fibrillation	R	20	4	1	25
	L	1	0	1	2
	B	(R>L) 1	2	0	3
		(L>R) 2	0	0	2
Chest taps	R	45	22	14	81
	L	4	2	4	10
	B	(R>L) 2	5	3	10
		(L>R) 2	0	0	2
Total taps		57	34	24	115
Average amt. fluid removed	R	1000 c.c. (45)	1050 c.c. (22)	1050 c.c. (14)	1050 c.c.
	L	1100 c.c. (4)	1050 c.c. (2)	1000 c.c. (4)	1050 c.c.
	BR	1100 c.c. (4)	1300 c.c. (5)	1200 c.c. (3)	1200 c.c.
	BL	1150 c.c. (4)	550 c.c. (5)	800 c.c. (3)	850 c.c.

* R=right, L=left, B=bilateral, BR=bilateral R>L, BL=bilateral L>R.

any one case were included in this study, regardless of whether both were performed on the same side or one on each of the two sides. Auricular fibrillation was present in 32 of this series of cases, 24 being in the rheumatic group, six in the coronary and only two in the hypertensive group. Twenty-five of these 32 cases were aspirated from the right chest only, two from the left chest alone and in five bilateral taps were done with a greater amount of fluid removed from the right cavity in three of these. In the rheumatic group 57 thoracenteses were performed on the 35 cases, 49 times on the right side and eight times on the left. In 45 instances the right chest alone was aspirated and in only four the left alone. There were four instances in which both sides were tapped. It is of interest that the amount of fluid removed at each thoracentesis was almost the same no matter which side was tapped. When a similar review was made of the 22 cases of coronary heart disease it was found that 34 chest taps were performed, 27 on the right side and seven on the left, 22 on the right side alone and two on the left alone. In five instances bilateral paracenteses were done although in each instance the right hydrothorax was greater than the left. It seems significant that

while the average amount of fluid aspirated, where only one side was explored, was 1050 c.c., in the five cases in which both sides were explored an average amount of only 550 c.c. was obtained from the left side and 1300 c.c. from the right. In the last group, consisting of 18 cases of hypertensive heart disease, 24 chest taps were performed, 17 on the right and seven on the left, 14 on the right side alone and four on the left alone. Three bilateral aspirations were done, and in each instance the amount of fluid removed from the right pleural sac was greater than that removed from the left, the average being 1200 c.c. from the right and 800 c.c. from the left. In summary, among the 115 thoracenteses performed on 75 cases of congestive heart failure, 93 were done on the right chest and 22 on the left, 81 on the right chest alone and 10 on the left alone. In the 12 instances where both sides were explored, only twice was the amount of fluid removed from the right side found to be less than that removed from the left side.

The second approach toward determining the distribution of hydrothorax was made on 52 consecutive cases which had had no previous thoracenteses and were analyzed from the roentgenological evidence alone (table 2). Of this group the 18 with rheumatic heart disease presented pure right hydrothorax in nine instances, pure left hydrothorax in three, and in six fluid occurred bilaterally and about equally on the two sides. In the 12 cases of coronary artery disease, right unilateral hydrothorax was present in three, and in the other nine fluid was present on both sides, predominantly right in four, predominantly left in two, and about equally in three. The 16 cases of hypertensive heart disease showed fluid in the right thorax only in six, and all the remaining presented fluid bilaterally, more on the right in four, more on the left in two, and about equally in four. No definite tendency

TABLE II
Hydrothorax in Congestive Heart Failure, Radiological Examination

Heart disease		Rheumatic	Coronary	Hypertensive	Misc.	Total
Site of hydrothorax	R	9	3	6	2	20
	L	3	0	0	1	4
		(R>L) 0	4	4	1	9
	B	(R=L) 6	3	4	1	14
		(L>R) 0	2	2	1	5
	Total	18	12	16	6	52
Site with Aur. Fib.	R	5	1	2	0	8
	L	1	0	0	0	1
		(R>L) 0	1	0	1	2
	B	(R=L) 4	1	1	0	6
		(L>R) 0	0	0	1	1

to a preponderance of fluid in either side of the thorax occurred in six cases of miscellaneous types of heart disease. Thus, of this entire series, 20 cases evidenced pure right hydrothorax, four pure left, with the remaining 28 presenting fluid on the two sides about equally, i.e. predominantly right in nine, predominantly left in five, and with no discernible difference in 14. Auricular fibrillation was present in 18 instances and of these 10 showed more fluid in the right chest, two in the left and in six it appeared to be equal. Unilateral hydrothorax in this group occurred approximately five times more often on the right side than on the left, and when the hydrothorax was bilateral there appeared no definite tendency for either side to predominate.

In the third study, 110 cases of congestive heart failure presenting hydrothorax at postmortem examination were analyzed (table 3), and the deductions were based on the amounts of fluid determined by direct measurement. It was realized that the agonal state might influence the formation of a terminal hydrothorax of limited degree, when the circumstances were favorable to such, and transudates of less than 300 c.c. were arbitrarily excluded from the study. A considerable number of these cases had had thoracenteses performed prior to death, and a quantitative analysis of the fluid so removed has been compiled for consideration.

The rheumatic group presented unilateral right hydrothorax twice, unilateral left three times, and in 50 the fluid was distributed bilaterally with the greater amount on the right in 44, on the left in four, and in two equally. In two of the three instances in which fluid occurred on the left side alone there was complete obliteration of the right pleural cavity by fibrous adhesions. Signs of left heart failure had dominated the clinical picture in five of the 55 cases, and in one of these fluid was found only on the left side, while on the other four it occurred bilaterally and predominantly right (3) or equal (1). Pulmonary infarction was present in 25 of this group and complicated left hydrothorax in three instances and right hydrothorax in one. In 21 cases so complicated, fluid was found in both cavities with the greater amount in the right in 20 of these. Prior to death auricular fibrillation had existed in 38 of the rheumatic patients, and of this number one showed fluid on the right side alone at autopsy, two on the left side alone and 35 presented fluid bilaterally with that on the right predominating in 33. The average amount of fluid found in the right pleural sac, in this rheumatic group, was 550 c.c. and that in the left sac was 350 c.c. Of similar interest is the fact that in 27 of this group of 55 cases, in which 73 clinical thoracenteses had been performed (57 right, 16 left), an average amount of 900 c.c. of fluid had been removed from the right thorax and 700 c.c. from the left thorax.

In this study, 25 cases of coronary heart disease presented hydrothorax entirely on the right in two instances, entirely on the left in one and in 22 it was bilateral with the right side predominating in 18, the left in three, and neither in one. Fibrous adhesions had completely obliterated the right pleural cavity in the one instance in which the fluid was limited to the left side. Nine of the 25 cases had presented the usual signs of marked left heart

TABLE III
Hydrothorax in Congestive Heart Failure, Post Mortem

Heart disease		Rheumatic	Coronary	Hypert.	Luetic	Total
Number		55	25	23	7	110
Average age		46	66	61	53	54
Site of hydrothorax	R	2	2	1	1	6
	L	3	1	1	0	5
		(R>L) 44	18	18	5	85
	B	(R=L) 2	1	0	0	3
		(L>R) 4	3	3	1	11
Site with lt. ht. failure	R	0	0	0	1	1
	L	1	1	1	0	3
		(R>L) 3	5	9	3	20
	B	(R=L) 1	1	0	0	2
		(L>R) 0	2	2	1	5
Site with pul. infarction	R	1	0	0	0	1
	L	3	0	0	0	3
	B	(R>L) 20	6	3	2	31
		(R=L) 1	0	0	0	1
Site with aur. fib.	R	1	0	0	0	1
	L	2	0	0	0	2
		(R>L) 33	4	3	0	40
	B	(L>R) 2	0	1	0	3
Average of fluid at PM	R	550 c.c.	550 c.c.	Above three groups considered together.		
	L	350 c.c.	400 c.c.			
Fluid removed during life	Cases	27	26			
	R	57	34			
	Taps					
	L	16	6			
	Av					
Amt	R	900 c.c.	950 c.c.			
	L	700 c.c.	900 c.c.			

failure before death, and of these one was the case of unilateral left hydrothorax, while the remainder showed fluid bilaterally, with that on the right predominating in five and that on the left in two. In six cases in which pulmonary infarction accompanied the hydrothorax the latter was found to be bilateral and predominantly right in all. Four of this group had had auricular fibrillation, and in all these the hydrothorax was also bilateral with the greater amount of fluid on the right side.

In 23 cases of hypertensive heart disease unilateral hydrothorax occurred only in two instances, once on each side, while bilateral hydrothorax occurred 21 times, in greater degree on the right in 18 and on the left in three. The right pleural space was completely obliterated by fibrous adhesions in the one case showing fluid on the left side alone. Signs of left heart failure had been the outstanding clinical features in 12 of the 23, and all these, except the case of left hydrothorax, presented fluid bilaterally with the greater amount in the right pleural cavity in nine, and in the left in two. In three cases where pulmonary infarction occurred the hydrothorax was bilateral and predominantly right sided in all. Auricular fibrillation had been present in four cases, and the hydrothorax was bilateral in all these, with that on the right greater in three.

Seven cases of syphilitic heart disease presented pure right hydrothorax in one, and in the other six it was bilateral, and predominantly right in five. Left heart failure had been outstanding in five of this group with one showing unilateral right hydrothorax and four showing fluid bilaterally with the greater amount on the right in three. In two cases evidencing pulmonary infarction the hydrothorax was bilateral and greater on the right side.

Because left heart failure had been clinically prominent in a relatively high percentage of the 55 cases, including the coronary, hypertensive, and syphilitic heart disease groups, these were conveniently considered together in calculating the average amount of fluid found in the two pleural sacs. Here again it was observed that the average amount of fluid found in the right sac (550 c.c.) exceeded that found in the left (400 c.c.). Likewise, 26 of these 55 cases had had 40 clinical paracenteses performed, 34 on the right chest and six on the left chest, with the removal of an average amount of 950 c.c. fluid from the right pleural cavity and 900 c.c. from the left.

This entire group of 110 cases of congestive heart failure, studied post mortem, presented hydrothorax on the right side alone in six instances, on the left side alone in five, and bilaterally in 99 or 90 per cent of cases. Of the latter there was found a greater amount of fluid in the right cavity in 85, more in the left cavity in 11 and in three it was equal. Complete obliteration of the right pleural space by fibrous adhesions could account for three of the five cases of pure left hydrothorax. It was thought that an extensive fibrous pleuritis, especially involving the lower portion of these membranes, might have influenced the distribution of the accompanying hydrothorax in 19 other instances, with involvement of the right pleura nine times, of the left three times, and of both right and left seven times. Only in rare instances did

such extensive pleural involvement suggest its presence either clinically or radiologically. Left heart failure had dominated the clinical picture in 31 cases. Among these the hydrothorax was unilateral and right in one instance, unilateral and left in three, and in the remaining 27 it was bilateral with the greater degree on the right in 20, on the left in five and in two it was equal. Recent pulmonary infarction had occurred in 36 cases, often presenting multiple areas, either unilateral or bilateral. In this group hydrothorax occurred on the right side alone in one instance, on the left alone in three, and bilaterally in 32 with a greater amount of fluid found in the right cavity in 31. In only rare instances did any close relation between the occurrence or distribution of hydrothorax and the presence of an infarctive process suggest itself. However, owing to the nature of the fluid, such cases might easily have been excluded from this study. In 1935 Joly² gave careful attention to this question and felt that pulmonary infarction seldom causes the formation of an extensive cardiac hydrothorax. Auricular fibrillation had been present in 46 cases, of which hydrothorax was limited to the right side in one, to the left side in two, while in 43 it was bilateral and predominantly right in 40. Although the percentage of occurrence of bilateral hydrothorax in this study was quite high, it would appear that the preponderant involvement of the right pleura was consistently evident regardless of the manner in which the cases were grouped for consideration.

The present observations and studies have led to findings which strongly support the general opinion in regard to the distribution of hydrothorax in congestive heart failure. Thus, when an analysis based on the incidence of thoracenteses was made, a marked tendency for the right chest to predominate the picture was encountered (table 1). In this series of cases one side of the chest was aspirated alone in 91 instances, 88 per cent being performed on the right thorax. When the hypertensive patients were considered as a group, the right thorax was aspirated in 71 per cent of instances. While this tendency was maintained, regardless of the underlying heart condition, it would appear that auricular fibrillation and other factors incident to rheumatic heart disease further favor a preponderance of right hydrothorax. In the second series of cases (table 2) as viewed by the roentgenologist, a greater amount of fluid was observed in the right pleural cavity in 56 per cent of instances and in 27 per cent it appeared to be about equal on the two sides. Although the number of cases considered here was quite small, there again appeared augmented influences favoring right hydrothorax in the rheumatic group. Published statistics on the distribution of hydrothorax, as determined at postmortem examination, appear to be in close agreement; however, the present series (table 3) indicated a greater percentage of bilateral hydrothorax than had been previously reported. This discrepancy may be partially accounted for by the manner of screening the subjects and by the use of different methods of recovering and considering the fluid. In 107 of this series of cases the amount of fluid removed from the right pleural cavity exceeded that removed from the left in 85 per cent.

This ratio varied between etiologial groups, being found highest in the rheumatic and lowest in the syphilitic, but in no instance did it fall below 80 per cent. These studies indicate that from whatever angle an analysis is attempted, regardless of the method of approach or the underlying cardiac condition, the combination of factors which determine the transudation of fluid into the pleural sacs exerts an influence in such a manner as predominantly to involve the right pleura. This influence, however, appears to become augmented in rheumatic heart conditions as compared to those in which failure of the left heart is more frequently encountered.

DISCUSSION

When one attempts to review the numerous efforts that have been made to explain the distribution of hydrothorax which occurs in the course of congestive heart failure, one is struck by the fact that the subject has been approached from isolated points of view. This has led to an over-emphasis of some particular factor involved and a tendency toward over-simplification of the problem as a whole. Much of the work published has been based on clinical observation of the condition with theoretical conclusions drawn as to the most likely factor determining the distribution of the fluid. In 1867 Bacelli³ advanced the azygos theory to explain the comparative frequency of right hydrothorax, assuming that pleural fluid accumulated through disturbance in the systemic circulation. His views seem to have been accepted without question until the turn of the century and indeed have made themselves felt until much more recently. In 1904 Steele,⁴ reviewing his earlier work (1896) and that of Stengel,⁵ reported the occurrence of right hydrothorax alone, or as greater than left, in 60 per cent of clinical cases and in 77 per cent of those observed at postmortem examination. He and Stengel felt that pressure on the root of the right lung and azygos vein by an enlarged right auricle could explain the predominance of right hydrothorax and suggested that the site of a hydrothorax was associated with a corresponding enlargement of the right or left side of the heart.

Crediting West⁶ with having expressed similar views previously, Fetterhoff and Landis⁷ in 1909 presented a convincing argument that transudation of fluid into the pleural sacs took place from the visceral rather than the parietal layer and therefore depended upon involvement of the pulmonary instead of the systemic circulation. They argued that pressure on the right or left pulmonary veins, by a dilated right or left auricle respectively, determined the location of the pleural transudate. Since the right auricle was more easily and consequently more commonly dilated than the left, a predominance of right hydrothorax might be expected.

More recently (1930) Satke⁸ presented experimental data demonstrating a greater relative degree of pressure negativity in the right pleural space, as compared to that in the left, in normal individuals, and suggested this difference would explain the prevailing tendency toward preponderance of

right hydrothorax. This tendency was supported by Famulari⁹ on the basis of the anatomical relations existing between the thoracic aorta and the hemiazygos vein and the presence of valves in the latter. Dock¹⁰ in 1935 presented convincing evidence that the anatomic and hydrostatic factors relating to the flow of blood from the pulmonary venous bed to the left ventricle strongly favored the predominance of right over left hydrothorax. He pointed out these factors as being considerably augmented by the right lateral decubital position which cardiac patients generally prefer, according to the studies on "trepopnea" by Wood, Wolferth and Terrell.¹¹

Fishberg¹² states that although cardiac hydrothorax is often unequal and usually right sided, no adequate explanation has been given to account for this distribution. He expresses the opinion that transudation into the pleural sacs, due to heart failure, depends upon disturbance of the systemic as well as the pulmonic circulation. In studying left heart failure, Bedford¹³ found left hydrothorax in 18 of 38 cases, whereas fluid occurred on the right side alone in only nine instances. Because of the unusual incidence of unilateral left hydrothorax in this series, in opposition to accepted views, Bedford and Lovibond (1941) did a follow-up study including all types of congestive heart failure.¹ They agreed with Steele's earlier idea that there existed a definite relation between the underlying heart condition and the site of the hydrothorax and reached conclusions to which reference has already been made. It is of interest that Weiss¹⁴ in his studies of pulmonary edema found that usually congestion and edema started in the right lung and remained more intense on this side than on the left.

The relative rôles played by the systemic and pulmonary circulations in the pathogenesis of cardiac hydrothorax has been a subject of much speculation and controversy. With the accumulation of clinical and experimental data, however, there seems little doubt that the visceral pleura is to be considered the source of such fluid collections. Graham¹⁵ in 1921, working on the edematous lung excised immediately post mortem, was able to demonstrate the transudation of fluid from the visceral pleura by varying the degree of pressure negativity within the range of normal. He was convinced that the increased pressure negativity produced by forcible inspiration could suck excess fluid through the surface of the lung. Zdansky¹⁶ expressed the view in 1929 that, on the basis of radiological evidence, hydrothorax should be considered as the sequence of pulmonary engorgement and edema. Extensive observations were reported by Yamada¹⁷ in 1933 on several hundred presumably healthy Japanese soldiers, in whom pleural fluid could be aspirated in 29 per cent, and following severe exercise in 70 per cent of the same group. One wonders whether a heightened negative intrathoracic pressure, acting alone, could account for such unusual findings. The amounts of fluid dealt with were too small to warrant an opinion as to its actual distribution.

That almost the entire capillary venous return from the visceral pleura is received by the pulmonary veins has been shown by Miller¹⁸ in 1937.

More recently Drinker,¹⁰ in his noted lectures on pulmonary edema and inflammation, tersely stated, "It is generally acknowledged that two factors are fundamental in causing transudation in the lungs and pleural sacs. They are, first, sustained increase in pulmonary pressure, and second, anoxia—while one or the other may be dominant in a given case, they never, in my opinion, work alone." After discussing the variation, from tissue to tissue, in increased capillary permeability due to anoxia and emphasizing the particular vulnerability of the lung capillaries to this and other influences, he further stated, "It is my belief, I cannot say conviction—that simple pulmonary edema and the more serious pulmonary exudations depend more upon alterations in the permeability of the lung capillaries than upon complicated pressure relations in the pulmonary circulation."

Accepting the view that the visceral pleura is the principal source of abnormal collection of fluid within the pleural sacs, and owing to their peculiar environment, their increased susceptibility to anoxia, and the inadequacy of pulmonary lymph flow under stress,¹⁹ that the pulmonary capillaries are particularly vulnerable to the forces promoting transudation, there are yet to be considered a number of anatomical and physiological factors which may determine, modify, or tend to localize such a process.

A number of these factors pertain to the lungs themselves. The right lung is some 10 per cent greater in volume than the left and, considering the extra lobe on the right, the disproportion between the areas of visceral pleura on the two sides is even greater. Diseases of the lungs or pleurae, active or healed, were considered by Zdansky¹⁶ and Weiss²⁰ to influence the localization of pulmonary edema and therefore its sequelae. Pleural adhesions may influence the accumulation of pleural fluid either positively or negatively, depending upon the extent of the involvement. Christie and Meakins²¹ in their studies on intrapleural pressure changes in congestive heart failure, were able to demonstrate marked decrease in distensibility and impairment in elasticity of the lungs. Working along similar lines, Prinzmetal and Kountz²² considered the occurrence of a vicious circle in the relation of pulmonary congestion to lung ventilation. Any factor then, which tends to limit respiratory excursion, such as hypostasis, hepatic engorgement, cardiac enlargement, etc., tears down the natural defenses against the consequences of local increased capillary transudation.

It is difficult to visualize local pressure effects on the pulmonary venous return by an enlarged right or left auricle. There seems to be no consistent relation between such enlargement and the site of a hydrothorax from the radiologic point of view. Of greater significance may be gross cardiac enlargement resulting in direct compression of lung tissue. It is clear that the onset of cardiac arrhythmia often initiates congestive failure, but the high incidence of right hydrothorax in the presence of auricular fibrillation, as brought out by Bedford and Lovibond, warrants further study. The pulmonary lymphatic drainage, as shown experimentally by Warren, Peterson and Drinker,²³ takes place almost entirely through the right lymphatic

duct with limited anastomosis to the thoracic duct. One wonders what effect this might have on the lungs individually when lymphatic stasis occurs and whether the left lung receives greater benefit from the collateral drainage. The elective position patients assume, as emphasized by Dock²⁴ and by Wood et al., further influences capillary leakage and lymphatic stasis as does also the anatomic and hydrostatic factors described by Dock. That a single factor, such as thrombosis of a blood vessel or obliteration of a pleural space, can explain the location of a pleural transudate is clearly understood, but such instances are relatively rare.

It is much more difficult to form an impression as to the relative importance of the parts played by the visceral and parietal pleurae in absorption of fluid, and little experimental work seems to have been done on which to base an opinion. That the visceral pleura is active in the absorption of fluid is apparent in instances of localized interlobar pleural effusions. It is reasonable to regard the mechanism of pleural fluid formation as one in which there is constantly a transudation and reabsorption of fluid in the pleural sac. When excessive amounts are present either or both factors may be disturbed and recovery take place when the normal balance is reestablished. In consideration of the problem it would seem advisable to keep the fundamental factors of transudation in the lungs and pleural sacs in mind and to realize that in a given case a number of influences may be active together in determining the site of fluid accumulation.

SUMMARY AND CONCLUSIONS

1. The distribution of hydrothorax in congestive heart failure was determined in three groups of patients by three methods respectively, i.e., by thoracentesis, by radioscopy, and at autopsy.

2. The findings obtained from these three analyses were in close general agreement throughout the study.

3. Depending on the method considered, right hydrothorax predominated in from 56 to 80 per cent of cases and left hydrothorax in from 12 to 17 per cent. Fluid was equally distributed in 3 to 27 per cent.

4. When etiological groups of heart disease were considered, the predominance of right hydrothorax over left was maintained regardless of the underlying heart condition.

5. Rheumatic heart disease and auricular fibrillation appeared to augment the influences determining a right hydrothorax, while pure left heart failure tended to mitigate these to a limited degree.

6. Any explanation for the distribution of hydrothorax in congestive heart failure may be attempted only through consideration of a number of influencing factors. However, it is clear that the balance of these forces is exerted in such a manner as greatly to favor the involvement of the right pleural sac.

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BIBLIOGRAPHY

1. BEDFORD, D. E., and LOVIBOND, J. L.: Hydrothorax in heart failure, *Brit. Heart Jr.*, 1941, iii, 91.
2. JOLY, F.: Les epancements pleuraux des cardiaques, Thèse de Paris, No. 679, 1935.
3. BACELLI, G.: *Patologia del cuore e dell'aorta*, Rome, 1867.
4. STEELE, J. D.: Hydrothorax in heart disease, *Jr. Am. Med. Assoc.*, 1904, xliii, 927.
5. STENGEL, A.: *Univ. Pennsylvania Med. Bull.*, Philadelphia, 1901, xiv, 103.
6. WEST, S.: *Diseases of the organs of respiration*, 1909, London.
7. FETTERHOFF, G., and LANDIS, H. R. M.: Compression of pulmonary veins, the pressure factor in the etiology of cardiac hydrothorax, *Am. Jr. Med. Sci.*, 1909, cxxxviii, 712.
8. SATKE, O.: Explanation of greater degree of hydrothorax on right side in congestive heart failure, *Ztschr. f. klin. Med.*, 1930, cxiii, 212.
9. FAMULARI, S.: On the mechanism of production of right hydrothorax in cardiopaths, *Riforma Med.*, 1933, xlix, 860.
10. DOCK, W.: The anatomic and hydrostatic basis of orthopnea and right hydrothorax in congestive heart failure, *Am. Heart Jr.*, 1935, x, 1047.
11. WOOD, F. C., JR., WOLFERTH, C. C., and TERRELL, A. W.: "Trepopnea" as an etiological factor in paroxysmal nocturnal dyspnea, *Am. Heart Jr.*, 1937, xiv, 255.
12. FISHBERG, A. M.: *Heart failure*, 1940, Lea and Febiger, New York.
13. BEDFORD, D. E.: Left ventricular failure, *Lancet*, 1939, i, 1303.
14. WEISS, S.: Pulmonary congestion and edema in heart disease, *Proc. New England Heart Assoc.*, Jan., 1941.
15. GRAHAM, E. A.: Influence of respiratory movements on formation of pleural exudates, *Jr. Am. Med. Assoc.*, 1921, lxxvi, 784.
16. ZDANSKY, E.: Beiträge zur Kenntnis der kardialen Lungenstrauung auf Grund roentgenologischer klinischer und anatomischer Untersuchungen, *Wien. Arch. f. inn. Med.*, 1929, xviii, 461.
17. YAMADA, S.: Über die Flüssigkeit in der Pleurahöhle der gesunden Menschen, *Ztschr. f. d. ges. exper. Med.*, 1933, xc, 342.
18. MILLER, W. S.: *The lung*, 1937, Chas. C. Thomas, Baltimore, Md.
19. DRINKER, C. K.: *Pulmonary edema and inflammation*, 1945, Harvard Univ. Press, Cambridge.
20. WEISS, S.: Unpublished observations.
21. CHRISTIE, R. V., and MEAKINS, J. C.: Intrapleural pressure in congestive heart failure, *Jr. Clin. Invest.*, 1934, xiii, 323.
22. PRINZMETAL, M., and KOUNTZ, W. B.: Intrapleural pressure in orthopnea, *Proc. Soc. Exper. Biol. and Med.*, 1934, xxxi, 610.
23. WARREN, M. F., PETERSON, D. K., and DRINKER, C. K.: The effects of heightened negative pressure in the chest, together with further experiments upon anoxia in increasing the flow of lung lymph, *Am. Jr. Physiol.*, 1943, cxxxvii, 641.
24. DOCK, W.: The evil sequelae of complete bed rest, *Jr. Am. Med. Assoc.*, 1944, cxxv, 1705.

THE MECHANISM AND PREVENTION OF CARDIO-VASCULAR CHANGES DUE TO INSULIN *

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ASIDE from troublesome hypoglycemic reactions insulin is generally considered a rather innocuous drug in therapeutic dosage. Joslin¹ and others² have alluded to dangers of insulin therapy in patients with cardiac disease, but very little attention has been paid to these warnings, and insulin is often dispensed to older diabetics in a care-free and almost routine fashion. Büdingen,³ von Noorden⁴ and others were impressed even at an early period by dangerous and sometimes fatal cases of anginal syndrome following insulin therapy in aging diabetics. Gigon⁵ reported the sudden death of a diabetic with heart disease after the third injection of insulin. Schönbrunner⁶ described severe electrocardiographic changes in a diabetic with heart disease, who had been treated with insulin for four days and whose blood sugar was 229 mg. per cent when these changes were present. Joslin⁷ reported a patient admitted in insulin shock, who on autopsy a few days later was found to have a fresh myocardial infarction. Within the past year we have observed three cases of acute myocardial infarction (confirmed at autopsy) which occurred immediately following an episode of hypoglycemia induced by insulin therapy in diabetics with atherosclerotic heart disease. The frequency of heart disease and its complications in diabetes mellitus is common knowledge, but one might be inclined to suspect the possible rôle of insulin as a factor in the high incidence of angina pectoris or coronary occlusion, which is five times as common in diabetics as in nondiabetics of the same age.⁸

Following the widespread use of insulin shock in the treatment of schizophrenia, further indications of the dangers of insulin therapy have become apparent. Schou⁹ reported 13 cases of serious cardiac complications in 375 patients treated with insulin shock. Gralnich¹⁰ described a patient who developed pulmonary edema and electrocardiographic changes resembling coronary occlusion during insulin shock. Others^{11, 12, 13, 14} emphasized circulatory changes as a danger of insulin shock therapy. One observer¹⁵ found no electrocardiographic changes in nine patients treated with insulin or metrazol.

In order to investigate the relationship of insulin and cardiovascular changes, the following studies were undertaken on a total of 18 patients.

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EXPERIMENTAL STUDIES

Experiment 1. Eight patients were used in this group; three were young individuals (18 to 35 years) with no evidence of heart disease, and five were older individuals (over 50 years); of these, two suffered from severe anginal syndrome and three were in actual congestive failure at the time these experiments were performed. The patients were placed on a high carbohydrate diet for several days, and then three studies were carried

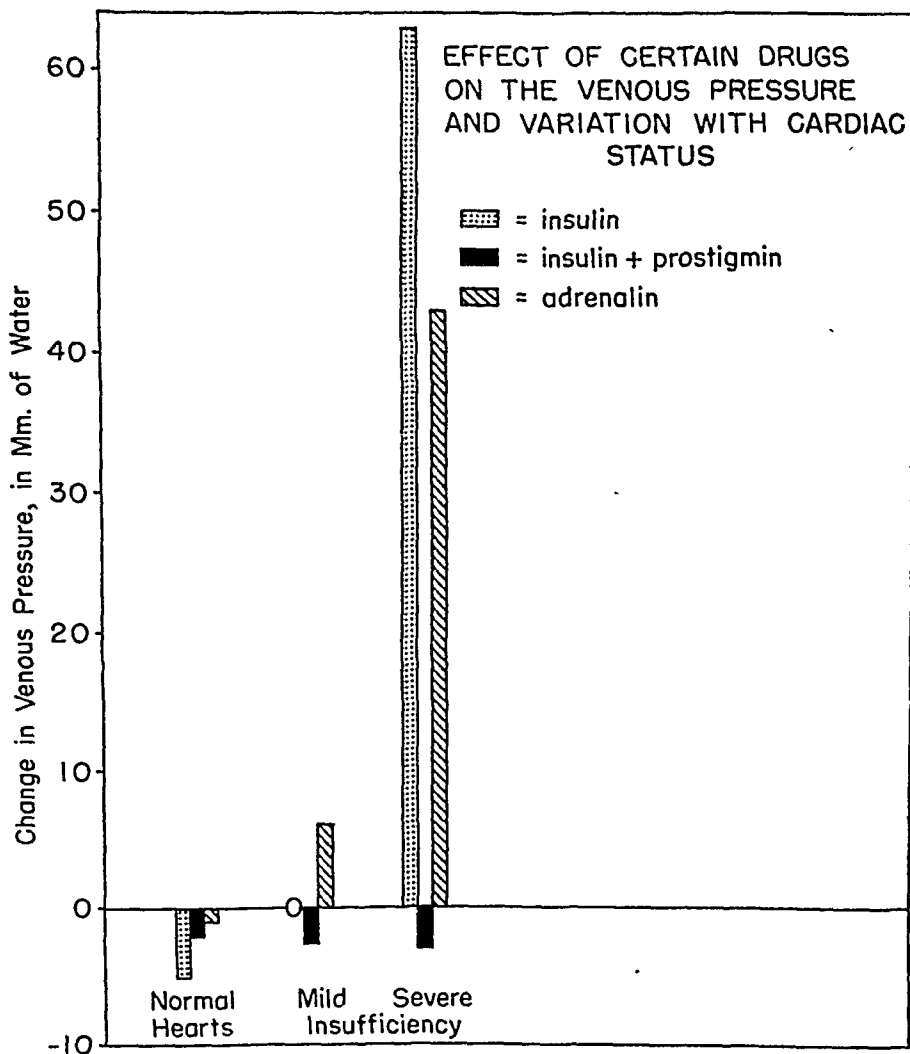


FIG. 1.

out on each one. First, 25 to 35 units (depending on the body weight) of regular insulin were given intravenously, and the blood sugar was allowed to fall to severely hypoglycemic levels (50 to 35 mg. per 100 c.c.). This state was maintained for two hours. On another day, each patient was given the same dose of insulin as before together with 1.0 mg. of prostigmin,⁶¹ and 15 minutes later 0.5 mg. of prostigmin was injected. On a third day each patient was given 10 minims of a 1:100 solution of adrenalin hydrochloride.

Control studies of respiration, blood sugar, blood pressure, pulse rate, venous pressure, ether and decholin circulation time, and electrocardiogram were made at the start and repeated every 15 to 30 minutes throughout the experiment.

Results. The effects of insulin and adrenalin on the blood sugar, blood pressure and pulse rate are too well known to deserve discussion; suffice it to say that our results were in full agreement with the established data.

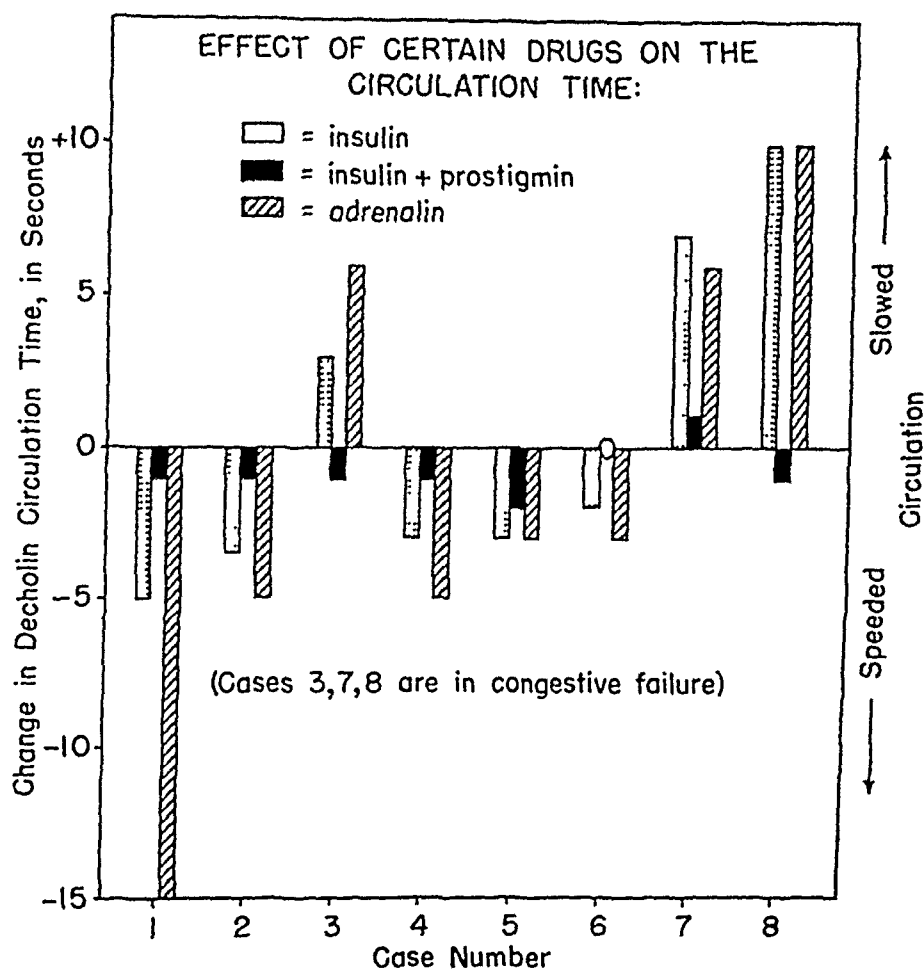


FIG. 2.

A. *Venous pressure.* The effect of these drugs on the venous pressure varied with the cardiac reserve as seen in figure 1. It is evident that in normal hearts and in hearts with mild diminution of the cardiac reserve, the changes were slight. In the severe cardiacs, however, profound and parallel alteration were induced by insulin and adrenalin. Prostigmin administered simultaneously with the insulin completely inhibited this change in all cases.

B. *Circulation time.* Figure 2 summarizes the data. Insulin hypoglycemia and adrenalin had essentially the same effect in every case, with the latter generally more effective. It is interesting to note that the circulation

was slowed only in those cases with congestive failure. Prostigmin counteracted the effect of insulin in every case, regardless of the direction of change.

C. *Heart rate.* Figure 3 shows a further effect of prostigmin. With insulin hypoglycemia, as with adrenalin, the heart rate rises gradually. The addition of prostigmin to the insulin not only prevented the increase in heart rate, but actually produced a slight bradycardia in most cases.

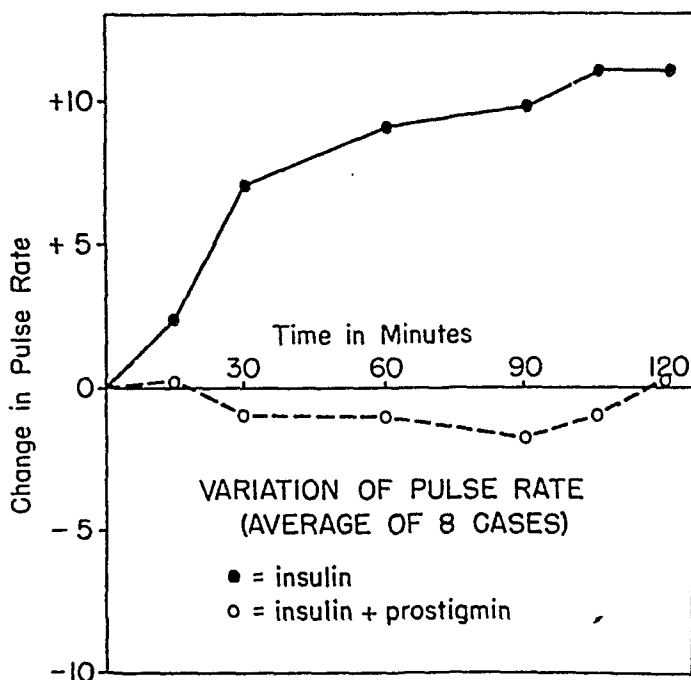


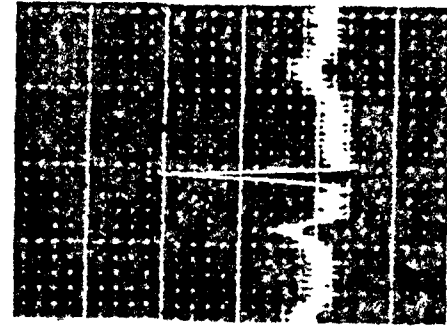
FIG. 3.

D. *Electrocardiographic changes.* In the three normal patients:

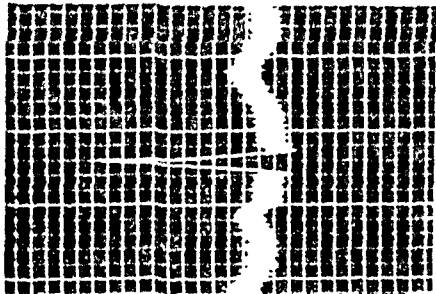
1. *Insulin alone* shortened the QRS interval once. ST was depressed once and the T-wave slightly depressed twice.
2. *Adrenalin* caused no appreciable changes.
3. *Insulin plus prostigmin* shortened PR once. There were no ST segment or T-wave changes.

In the group of five cardiacs, changes were far more pronounced.

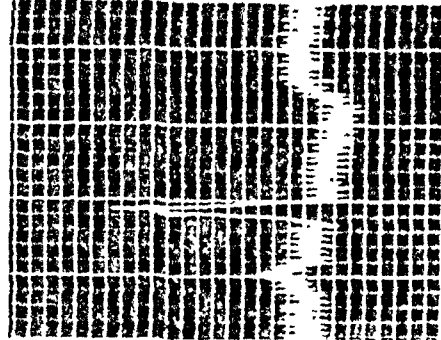
1. *Insulin alone* lowered P twice, shortened PR twice. No widening of QRS, as seen by other investigators, was observed in our material. The ST segment was elevated in three cases and accompanied an inversion of T.
2. *Adrenalin* elevated the ST segment in two cases, depressed ST in one, and produced T inversion once. Aside from actual inversion of T, both insulin and adrenalin changed the upright T-wave to one more round-shouldered, symmetrically-limbed, simulating the type of change observed in coronary insufficiency (see figure 4). These alterations were produced in almost parallel fashion by insulin and adrenalin.



A. 1.

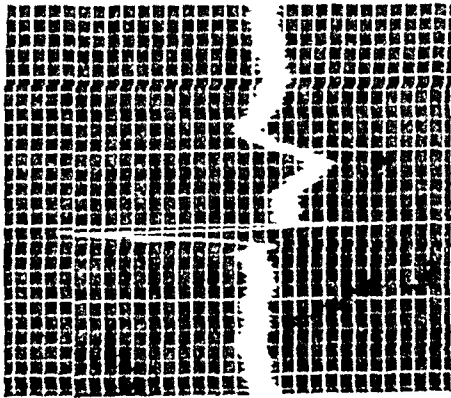


2.

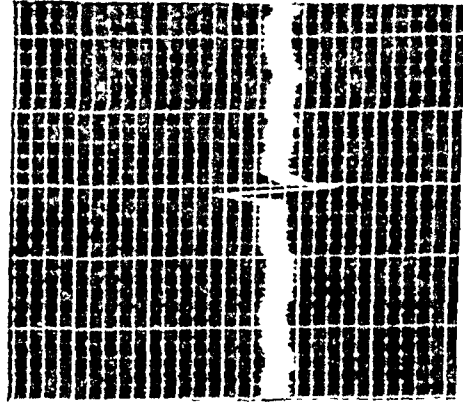


3.

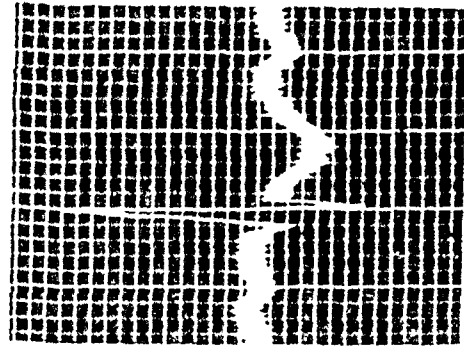
4.



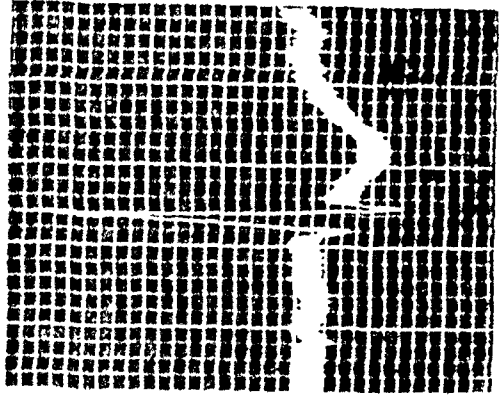
B. 1.



2.



3.



4.

FIG. 4.

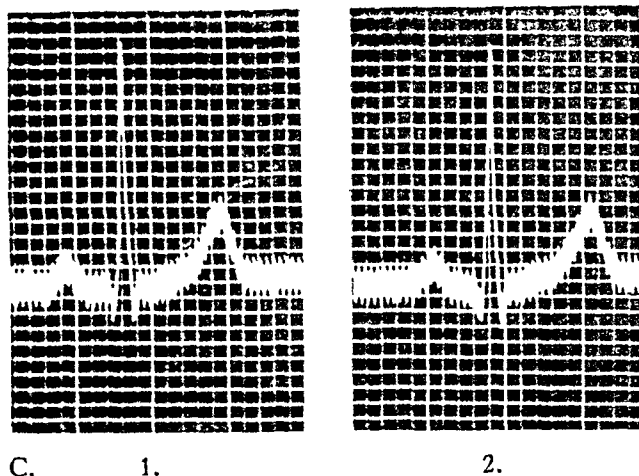


FIG. 4. *Experiment 1.* A: 1. Control EKG before insulin hypoglycemia. 2. During insulin shock. 3. Control EKG before adrenalin. 4. After adrenalin injection.

With insulin, observe: elevation of ST segment; T-wave becomes peaked, symmetrically limbed with round, sloping shoulders. Almost identical changes occur with adrenalin.

B: 1. Control EKG before insulin hypoglycemia. 2. During insulin shock. Control EKG before insulin-prostigmin. 4. During insulin-prostigmin hypoglycemia.

With insulin, observe: Decreased amplitude of QRS with more pronounced S-type configuration; elevation of ST segment; flattening of diphasic T-wave. Note that none of these changes appears during hypoglycemia following insulin-prostigmin.

Experiment 2. C: 1. Control EKG. 2. Two hours after insulin plus glucose (blood sugar level elevated 15 mg. per cent). No sympathetic stimulation. Observe that EKGs are identical.

3. *Insulin plus prostigmin* caused no alteration of the electrocardiogram in any instance.

Experiment 2. Five healthy young adults (18 to 35 years) and five older patients (over 50 years) with moderate or advanced diminution of cardiac reserve were used. After a control electrocardiogram, each patient was given a mixture of 25 U. regular insulin and 50 gm. glucose intravenously, as well as 400 gm. glucose in grapefruit juice by mouth. Serial electrocardiograms and blood sugar determinations were made for two hours.

Results. The amount of glucose administered maintained the blood sugar level at least 10 mg. per 100 c.c. higher than the starting level in every case. No tachycardia or other evidence of sympathetic stimulation was noted although these signs were watched for carefully. The results were uniform: in no instance did any electrocardiographic change occur within two hours following insulin injection. (See figure 4.)

DISCUSSION

In order to evaluate these experiments properly, a brief review of the background of this problem is necessary.

Pathology. In the course of their studies on insulin shock, Hadorn and Walthard¹⁶ investigated the effect of insulin on the rabbit's heart. The findings in 47 animals led them to conclude that neither single injections of insulin nor insulin shock produced any anatomically demonstrable injury

of the myocardial fibers. Meessen¹⁸ reported disseminated necroses of the myocardial fibers in rabbits surviving the injection of insulin for 24 hours. Negri¹⁷ found similar necroses as well as patchy or diffuse cellular infiltration in both insulin-treated and control animals; he ascribed these changes to an infection common in rabbits, and did not believe that they were in any way related to the treatment with insulin. Tannenberg¹⁹ investigated this problem in a somewhat different manner, giving animals repeated daily doses of insulin in varying amounts. The muscle fibers showed swelling and hydropic degeneration and there were localized vasodilatations and constrictions. No necroses or infiltration were found. Tannenberg's data indicate that these changes probably disappeared in two or three days. In view of the transitory nature of the electrocardiographic changes which have been associated with insulin treatment, it seems far more likely that any histologically demonstrable alteration of the muscle fibers would be of the reversible character that Tannenberg describes rather than irreversible necrosis or infiltration.

The Effect of Insulin Injections on the Circulatory System. Many investigators have studied the effects of insulin injections on the circulatory system.^{20, 21, 22, 23, 24, 25, 26} A tachycardia, appearing one-half to one hour after injection; has been observed uniformly. Changes in blood pressure were usually found, with a rise of the systolic and a fall of the diastolic pressure. Though both effects did not always occur together, an elevated pulse pressure resulted consistently. Venous pressure and venous oxygen content both increased. All investigators concurred in finding an increased cardiac output, stroke volume, or other index of increased cardiac work. Studies of the electrocardiographic changes have been equally numerous.^{13, 17, 20, 21, 24, 25, 30, 30} In man, arrhythmias and extrasystoles were uncommon. Generally a small P, widening of the QRS complex, depression of the ST segment and flattening or inversion of the T-wave appeared. Many investigators observed the lack of correlation between the blood sugar level and the electrocardiographic changes. One³⁰ described a patient who showed no clinical symptoms with a blood sugar of 52 mg. per 100 c.c. and whose electrocardiogram remained unchanged. Another¹⁹ reported a patient who showed changes simulating infarction during routine insulin shock therapy. Two investigators^{15, 24} saw no "important" electrocardiographic changes and one of these²⁴ found no persistent changes even after repeated episodes of insulin hypoglycemia.

Clearly, the circulatory system is intimately affected by the injection of insulin. The explanation of these phenomena is in many respects still obscure. In general, three theories have been offered for the action of insulin on the circulatory system:

1. The effects are due to hypoglycemia.
2. The effects are due to insulin itself.
3. The effects are due to adrenalin discharge and to stimulation of the sympathetic nervous system.

The Hypoglycemia Theory. The most obvious solution of this problem was to associate the lowered blood sugar with the cardiac manifestations. The diminution of the food supply of the heart muscle was generally thought to be an important factor.¹⁴ This belief was based on rather fragmentary knowledge of cardiac metabolism, as has been shown by Evans,²⁷ McGinty and Miller²⁸ and others. These authors have demonstrated that heart muscle does not utilize glucose directly, or does so to a minor extent. By contrast, the heart removes considerable amounts of lactate from the blood; pyruvate, β -hydroxy-butyric acid and certain fats can also be metabolized. Cardiac glycogen is apparently used only as an emergency substance or is normally replaced as fast as it is used up. Thus it would appear that there is not such a critical lack of cardiac fuel as was originally supposed. A second important point, one that has been observed by many investigators,^{13, 21, 28, 31} is that there is no correlation between the clinical picture and the blood sugar level. Moreover, the electrocardiographic changes are not necessarily reversed by glucose^{21, 31} and may even increase during subsequent hyperglycemia.²⁵ Perhaps the most conclusive proof was furnished by Costedoat and Aujaleu³² who found no electrocardiographic changes whatever in rabbits with severe hypoglycemia induced by phlorizin poisoning. Soskin and his coworkers³¹ found that electrocardiographic changes occur in eviscerated dogs when the blood sugar falls below 30 mg. per 100 c.c. It is doubtful if this observation has any direct bearing on the changes observed in man.

Costedoat et al.³³ also disproved the hypothesis that glycogen depletion of the heart muscle—which may occur during insulin hypoglycemia^{34, 35, 36}—is responsible for the electrocardiographic changes. Complete depletion of the cardiac glycogen was produced in rabbits by phlorizin without any corresponding alterations of the electrocardiogram.

The Insulin Theory. Various observations have been cited to prove that insulin has a direct effect on the heart. Citron³⁷ has demonstrated transitory electrocardiographic changes in the frog's heart perfused with insulin. The patient described by Schönbrunner⁶ (see above) has often been cited as proof. However, it must be pointed out that a blood sugar of 229 mg. per 100 c.c. at some time during insulin therapy does not preclude the possibility of previous unnoticed sympathetic stimulation. The persistence of electrocardiographic changes after the restoration of a normal blood sugar level does not prove a direct effect of insulin, but merely indicates that the electrocardiographic changes are not as rapidly reversible as the blood sugar level. Moreover, the electrocardiograms of Soskin et al.³¹ indicate that tachycardia—and possibly other evidences of sympathetic stimulation—were present. Von Haynal et al.²¹ claimed to have obtained electrocardiographic changes although the blood sugar level was maintained. Examination of the protocols reveals that the blood sugar was allowed to drop 20 mg. per 100 c.c. or even more before relatively scanty amounts (6.6 to 16.0 gm.) of glucose were given. Elevation of the pulse rate in several instances suggests strongly that the rôle of the sympathetic system was not excluded by

these experiments. When adequate precautions against this side-effect are taken, our findings indicate that no electrocardiographic changes appear.

Certain other properties of insulin have not heretofore been considered in relation to their cardiovascular implications. Insulin exerts a powerful tissue-hydrating effect, either directly or indirectly.^{38, 39, 40, 41} Excessive tissue hydration and interstitial edema are capable of producing both functional and electrocardiographic changes, as seen for instance in myxedema. Insulin also has a tendency to liberate intracellular potassium.³⁸ Chronic potassium deficiency produces cardiac failure⁴³ and myocardial changes due to potassium deficiency in man have been described.⁴⁴ However, adrenalin itself also liberates intracellular potassium.⁴² The importance of tissue hydration and cellular potassium depletion, whether produced by insulin or adrenalin, is still an unexplored question. It is entirely possible that certain persistent cardiac changes may be due to this factor. The short-term changes studied in our experimental material were readily inhibited by a parasympathomimetic drug (prostigmin), and hence do not require alterations of electrolyte metabolism for their explanation. That such changes may exist, however, is neither suggested nor negated by our material.

The Autonomic Theory. The brilliant work of Cannon and his group²⁹ has served to elucidate an extremely important factor in this problem. They found that insulin hypoglycemia was not accompanied by tachycardia or blood pressure changes in the experimental animal if the heart was denervated and the adrenals removed. Adrenalectomy without heart denervation did not abolish these changes, showing that the entire sympathetic (that is, adrenergic) system was involved. The sympathetic stimulation produced by hypoglycemia was promptly reversed by the intravenous administration of glucose.

Clinically, the symptoms of insulin hypoglycemia are strikingly similar to those following the injection of adrenalin, and this point has been emphasized repeatedly.^{45, 46} The final proof was supplied by Brandt and Katz⁴⁷ who demonstrated the presence of increased amounts of adrenalin-like substances in the blood during insulin hypoglycemia.

Hadorn¹⁸ has described inversion of the T-wave following the injection of adrenalin. Knowing the sympatholytic effects of ergotamine, Kugelmann²⁹ administered both ergotamine and insulin to animals and found that 40 per cent failed to show the usual vascular changes although the blood sugar was lower than that of the controls. On the other hand, both ergotamine¹⁸ and atropine³⁷ increase and prolong the electrocardiographic changes induced by insulin. The explanation and significance of these paradoxical observations is not clear at the present time.

From the literature we have summarized and from our own investigations it appears that the hypoglycemic theory of the insulin cardiac effects fails to account for the observed phenomena, except under the special circumstances of Soskin's experiment. Some investigators believe that the electrocardiographic changes are produced by insulin itself. As has been

shown, the evidence in the literature for this hypothesis is not convincing, and our studies fail to substantiate it in any respect. On the other hand, both the studies of other investigators and the material presented in this paper confirm the essential identity of the cardiovascular effects of insulin and the sequelae of sympathetic stimulation. It is most likely, therefore, that a drop in blood sugar induced by insulin elicits adrenalin discharge from the adrenal medulla as well as direct cardiac stimulation via the sympathetic nerves to the heart. Our findings show that prostigmin counteracts the effects of this stimulation; the mechanism of this effect is not entirely clear. Two possible explanations suggest themselves: first, that prostigmin prevents adrenalin production and second, that prostigmin prevents the normal cardiac response to adrenalin. Prostigmin simply inhibits the activity of cholinesterase; it is not known to interfere with the production of adrenalin. In fact the opposite may be expected in the presence of increased amounts of acetyl choline, upon which the production of adrenalin depends. The second possibility therefore seems more likely: the increased parasympathetic activity decreases the responsiveness of the receptor organ (i.e., the heart) to the presumably unaltered discharge of adrenalin and sympathin.

There exists some controversy over the significance of the ST and T-wave changes seen with insulin hypoglycemia. Some workers, citing their reversibility, minimize the importance of these alterations. Hadorn and others believe that they are to be considered as actual evidence of myocardial damage despite their reversibility. It must be pointed out that these changes are nonspecific; identical, transitory changes can be produced by temporary, mild anoxia in patients with even a minimal decrease of the cardiac reserve.⁴⁹ Far more important in our eyes is the indisputable fact that the sympathetic stimulation which evidently causes these changes also increases cardiac work—an obviously undesirable and potentially harmful feature. With the establishment of this fact, the question becomes more or less academic.

We believe that certain rather practical recommendations follow from these experiments. It seems to be clear that the harmful effects of insulin therapy—that is, the increased cardiac work—can be counteracted by prostigmin. It is possible that the routine combination of these two drugs would be of value in the treatment of diabetics with diminished cardiac reserve. The method of diabetic control advocated by Joslin and his school employs diets and insulin calculated with great exactitude. Whereas this method may be theoretically preferable and actually feasible in specially equipped institutions, it involves manifest hazards and practical difficulties in the vast majority of ambulatory diabetics. With the unpredictable variation in energy requirements due to environmental influences it is almost inevitable that the blood sugar level should vary sufficiently to produce compensatory sympathetic activity at some time. The undesirability of such a reaction, in view of the foregoing data, is obvious. In this respect, a method of diabetic control as suggested by Tolstoi et al.⁵⁰ appears distinctly

superior: carbohydrate in excess of the calculated requirement is permitted and there is no concern over the spillage of the excess sugar. With this method, there is far less chance for the development of hypoglycemic sympathetic stimulation.

SUMMARY

The effects of insulin on the heart rate, venous pressure, circulation time and electrocardiogram were investigated and found to be essentially identical with those of adrenalin.

The administration of insulin with the maintenance of an unlowered blood sugar and the absence of sympathetic stimulation produced no electrocardiographic changes. It follows that the changes observed with insulin alone are due to sympathetic stimulation secondary to the insulin-induced hypoglycemia.

Attention is called to the dangers of insulin therapy in patients with heart disease, as borne out by three personally observed and autopsied cases of acute myocardial infarction immediately following an episode of insulin hypoglycemia.

The cardiovascular effects of insulin injection may be counteracted by the simultaneous administration of prostigmin.

The possible advantages of combined prostigmin-insulin therapy in diabetics with diminished cardiac reserve are suggested.

We wish to acknowledge our indebtedness to Dr. Walter Bense and to Dr. Otto Loewi for their invaluable suggestions as to the presentation of this material.

BIBLIOGRAPHY

1. JOSLIN, E. P., ROOT, H. F., WHITE, P., and MARBLE, A.: The treatment of diabetes mellitus, 1940, Philadelphia.
2. SOSKIN, S., KATZ, L. N., STROUSE, S., and RUBINFELD, S. H.: The treatment of elderly diabetic patients with cardiovascular disease; available carbohydrate and blood sugar level, *Arch. Int. Med.*, 1933, li, 122-142.
3. BÜDINGEN, T.: *Zentralbl. f. Herzkrankh.*, 1925, xvii, 215-224 and 231-240.
4. VON NOORDEN, H.: *Die Zuckerkrankheit*, 1927 (8th Ed.), p. 307.
5. GIGON, A.: Diabetes und Insulintherapie, *Klin. Wchnschr.*, 1923, ii, 1670-1671.
6. SCHÖNBRUNNER, E.: Über ein Fall von Schädigung des Herzens durch Insulin, *Med. Klin.*, 1935, xxxi, 1571-1572.
7. See Ref. 1, p. 444.
8. ROOT, H. F., BLAND, E. F., GORDON, W. H., and WHITE, P. D.: Coronary atherosclerosis in diabetes mellitus; postmortem study, *Jr. Am. Med. Assoc.*, 1939, cxiii, 27-30.
9. SCHOU, H. I.: Complications concerning shock therapy, *Acta Psych. et Neurol.*, 1942, xvii, 277-297.
10. GRALNICH, A.: Pulmonary edema and EKG findings resembling coronary occlusion in insulin treatment, *Psych. Quart.*, 1944, xviii, 650-659.
11. SALM, H.: Benommenheitszustände in Anschluss an die Insulinschockbehandlung von Schizophrenen, *München. med. Wchnschr.*, 1937, lxxxiv, 1046-1048.
12. MÜLLER, M.: Le traitement de la schizophrénie par l'insuline, *Ann. Med. Psychol.*, 1936, xciv (2), 649-658.

13. HADORN, W.: Untersuchungen über die Beeinflussung des Herzens durch Insulin und Hypoglykämie, *Ztschr. f. klin. Med.*, 1936, cxxx, 643-659.
14. MESSINGER, E.: Cardiovascular changes associated with insulin shock treatment, *Ann. Int. Med.*, 1938, xii, 853-866.
15. SONENTHAL, I. R., and LOW, A. A.: EKG studies after treatment with insulin and metrazol shock, *Jr. Nerv. and Ment. Dis.*, 1940, xci, 423.
16. HADORN, W., and WALTHARD, B.: Experimentelle Untersuchungen über anatomische Herzmuskelveränderungen in Insulinschock, *Ztschr. f. d. ges. exper. Med.*, 1939, cv, 174-179.
17. NEGRI, A.: Experimentelle Untersuchungen über die Wirkung höher Insulindosen auf das Myokard von Kaninchen, *Ztschr. f. d. ges. exper. Med.*, 1942, cxi, 69-88.
18. MEESSEN, H.: *Arch. f. Kreislaufforsch.*, 1940, vi, 361.
19. TANNENBERG, J.: Pathological changes in heart, skeletal muscle, and liver in rabbits treated with insulin in shock dosage, *Am. Jr. Path.*, 1939, xv, 25-53.
20. WITTGENSTEIN, A., and MENDEL, B.: Die Veränderung der T-Zacke des EKG während der Insulinwirkung, *Klin. Wchnschr.*, 1924, iii, 1119-1121.
21. VON HAYNAL, E., VIDOVSZKY, L., and GYÖRGYI, G.: EKG Untersuchungen über Insulinwirkung auf das Herz, *Klin. Wchnschr.*, 1928, vii, 1543-1549.
22. ERNSTENE, A. C., and ALTSCHULE, M. D.: The effect of insulin hypoglycemia on the circulation, *Jr. Clin. Invest.*, 1931, x, 521-528.
23. WIECHMANN, E., and KOCH, F.: Untersuchungen über den Hypoglykämischen Zustand nach Insulininjektion, *Deutsch. Arch. f. klin. Med.*, 1929, clxiii, 176-201.
24. GOODRICH, E. B., and JANNEY, F.: Insulin hypoglycemia and the electrocardiogram, *Jr. Nerv. and Ment. Dis.*, 1941, xciv, 10-16.
25. LAUTER, S., and BAUMANN, H.: Kreislauf und Atmung in Hypoglykämischen Zustand, *Deutsch. Arch. f. klin. Med.*, 1929, clxiii, 161-175.
26. KUGELMANN, B.: Zur Frage der Adrenalinausschüttung bei der Insulinhypoglykämie und bei Palsschen Gefäßkrisen, *Klin. Wchnschr.*, 1933, xii, 1488-1489.
27. EVANS, C. H. LOVATT: Metabolism of the heart, *Edinburgh Med. Jr.*, 1939, xlvi (2), 733-749.
28. MCGINTY, D. A., and MILLER, A. T., JR.: Studies on coronary circulation, absorption of lactic acid and glucose, and gaseous exchange of heart muscle, *Am. Jr. Physiol.*, 1932, ci, 76 (proc.) and 1933, ciii, 712-720.
29. CANNON, W. B., MACIVER, M. A., and BLISS, S. W.: Studies on the conditions of activity in endocrine glands, *Am. Jr. Physiol.*, 1924, lxix, 46-78.
30. VON HAYNAL, E.: Untersuchungen über Insulinwirkung auf das Herz, *Klin. Wchnschr.*, 1925, iv, 403-405.
31. SOSKIN, S., KATZ, L. N., and FRISCH, R.: The dual nature of the action of insulin upon the heart, *Ann. Int. Med.*, 1935, viii, 900-906.
32. COSTEDOAT, A., and AUJALEU, E.: Action de l'hypoglycemia sur l'electrocardiogramme du lapin, *Compt. rend. Soc. de biol.*, 1932, cx, 755-756.
33. COSTEDOAT, A., DEBUCQUET, L., and AUJALEU, E.: L'action de la phlorizin sur le coeur du lapin, *Compt. rend. Soc. de biol.*, 1932, cx, 756-757.
34. DUDLEY, H. W., and MARRIAN, G. F.: The effect of insulin on the glycogen in the tissues of normal animals, *Biochem. Jr.*, 1923, xvii, 435-438.
35. HETENYI, G.: Experimentelle Untersuchungen über den Mechanismus der Insulinwirkung, *Ztschr. f. d. ges. exper. Med.*, 1925, xlv, 439-441.
36. PEYER, G.: Der Gehalt der Kaninchenorgane an reduzierender Substanz bei verschiedenem Blutzuckerspiegel, *Biochem. Ztschr.*, 1929, ccvi, 3-15.
37. CITRON, J.: Experimentelle Beiträge zur Insulinwirkung, *Med. Klin.*, 1924, xx, 1362-1365.
38. STAUB, H.: *Insulin*, 1925, Berlin, p. 64-67.
39. KLEIN, O.: Hormones and water metabolism in diabetes after insulin and pituitary extracts, *Ztschr. f. klin. Med.*, 1924, c, 458-477.

40. KLEIN, O.: Further studies concerning insulin and water balance, *Med. Klin.*, 1925, xxi, 1116-1120.
41. YANNET, H.: Effect of prolonged insulin hypoglycemia on distribution of water and electrolytes in brain and muscle, *Arch. Neurol. and Psych.*, 1939, xlii, 237-247.
42. KEYS, A.: Response of plasma potassium level in man to administration of epinephrine, *Am. Jr. Physiol.*, 1938, cxxi, 325-330.
43. CLEGHORN, R. A., ARMSTRONG, C. W. J., and AUSTEN, D. C.: Clinical and chemical observations on adrenalectomized dogs maintained by diet high in sodium salts and low in potassium salts, *Endocrinology*, 1939, xxv, 888-892.
44. GOODOF, I. I., and MACBRYDE, C. M.: Heart failure in Addison's disease with myocardial changes of potassium deficiency, *Jr. Clin. Endocrinol.*, 1944, iv, 30-34.
45. GEÖRGI, F.: Humoral-pathologische Bemerkungen zur Insulinschocktherapie bei Schizophrenen, *Schweiz. med. Wchnschr.*, 1936, xvii, 935.
46. GROSS, M.: Insuline et Schizophrenie, *Schweiz. med. Wchnschr.*, 1936, xvii, 961.
47. BRANDT, F., and KATZ, G.: Über den Nachweis von Adrenalinsekretion beim Menschen, *Ztschr. f. klin. Med.*, 1933, clxxiii, 40-50.
48. ASK-UPMARK, E.: Der Einfluss des Prostigmins auf das normale Elektrokardiogram, *Ztschr. f. Kreislaufforsch.*, 1941, xxxiii, 41-48.
49. LARSEN, K.: Effect of anoxemia on the human electrocardiogram, *Acta med. Scandinav. (Suppl.)* 1936, lxxviii, 141-149.
50. TOLSTOI, E., ALMY, T. P., and TOSCANI, N.: Treatment of diabetes mellitus with protamine insulin: is a persistent glycosuria harmful? Metabolic study of a severe case, *Ann. Int. Med.*, 1942, xvi, 893-903.

DICOUMAROL THERAPY *

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1. This study discusses the factors concerned with dicoumarol therapy.
2. The initial dosage and a practical way of estimating maintenance dosage are shown.
3. The daily plasma prothrombin times, factors affecting them, and the need for dependable laboratory technic are emphasized.
4. The variation in degree of response, the lag period, and the therapeutic level are discussed.
5. Hemorrhage, the only toxic manifestation of dicoumarol, is considered, and the methods of treatment are stated.
6. The contraindications are listed.
7. The results of therapy in 60 patients including 13 cases of pulmonary embolism are discussed.

The rationale for dicoumarol therapy is based on the pathology of thrombosis, thrombophlebitis, and embolism as set forth in numerous papers. The insidious development of venous thrombosis and its unpredictable behavior are the chief causes for controversy concerning their treatment.^{1, 2} Frequently pulmonary embolism is the first sign of phlebothrombosis,³ and not uncommonly a day or two passes before signs and symptoms reveal its site. Here the clot is soft, friable, and poorly organized. It is easily detached from the vessel wall to float away in the venous current.⁴ Its highest incidence is in the calf muscles,⁵ although the feet, thighs, and pelvis may also be involved. The physically more impressive thrombophlebitis, as exemplified by "milk leg," is manifested by multiple signs and symptoms¹ and yet is the least dangerous of the clotting processes, for here the thrombus is organized and well attached. Only by extension and propagation does it offer a threat of embolism through formation of a fresh loose friable clot. One may surgically ligate the femoral vein to shut off this process, only to have it resume proximally.⁶ Where the site of thrombosis is not determined, one would be forced to do a bilateral femoral vein interruption. Studies have shown that patients over 40 years of age confined to bed for either surgical or medical reasons commonly have bilateral phlebothrombosis.⁷ In cases of pelvic phlebitis, surgical treatment is obviously impossible. Surgical ligation of the femoral vein is a method of prophylaxis of pulmonary embolism leaving much to be desired. It may not stop the process from extending, it may require bilateral ligation, and it has no place in therapy other than that involving the legs. In addition to its inadequacies, it carries a morbidity in the

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form of edema which in a series of 202 cases was immediate in 47.5 per cent and late in 42 per cent.

Early in the war it was realized that the morbidity and mortality from thrombophlebitis and pulmonary embolism would be high at a surgical center treating patients with major trauma from high velocity projectiles and crush injuries. Preliminary reports on dicoumarol¹⁰ by the Mayo Clinic group,⁸ Wright,⁹ Bingham,¹⁰ and others offered a possible solution. With their experiences as a guide, this therapy was adopted for use in all cases of embolism, thrombosis and phlebitis.

Dicoumarol acts as an anticoagulant by inducing hypoprothrombinemia, probably through inhibiting the formation of prothrombin in the liver. It may, to some degree, prolong the coagulation time of the blood, but this factor is variable and cannot be used as a means of judging the drug's action. At therapeutic prothrombin levels clotting does not occur, and the vessels of the entire body are protected from thrombosis.^{11, 12} Although clots that are already present probably cannot be affected, they cannot extend and propagate. Since emboli arise from new fresh thrombi only, their development is prevented. The great criticism leveled at dicoumarol is the delay in its effect,¹³ for after the initial dosage there is a lag period of 24 to 72 hours in the development of hypoprothrombinemia during which the patient is not protected from thrombosis. Statistical evidence shows that for some unknown reason, this theoretically justified criticism is not a factual threat. In the present series and in those of other investigators, it was found that no emboli occurred subsequent to institution of therapy. Barker et al.¹⁴ state "In dealing with patients who have had thrombophlebitis or a small pulmonary embolism we have rarely used heparin in addition to dicoumarol and have almost never encountered a second episode of thrombosis or embolism during the one to three days which elapsed between the beginning of administration of dicoumarol and the development of adequate prothrombin deficiency." However, there have been isolated cases reported where thrombosis occurred even during adequate hypoprothrombinemia. In the present study, one case developed thrombophlebitis in a small segment of a superficial vein in the midst of a three week period when the prothrombin level was steadily between 20 and 30 per cent, while the other 59 cases, including 13 with initial symptoms of pulmonary embolism, showed no signs of further vascular involvement. Dicoumarol in dosages that maintain a therapeutic blood prothrombin level is therefore an effective drug in preventing thrombosis. It follows that it is indicated as a prophylactic measure in post-operative patients with a history of phlebitis or embolism where the incidence of recurrence was 43.8 per cent and of subsequent fatal pulmonary embolism 18.3 per cent in cases not receiving dicoumarol.¹⁵

The prerequisite for dicoumarol therapy is the establishment of a test for blood prothrombin time which is accurate and dependable. The most reliable method is Quick's¹⁶ or one of its modifications. The one first used in this study was the Russel viper venom modification.¹⁷ Later, because of the

scarcity of this agent, tissue extract thromboplastin was used. By both methods the normal and the 10 per cent dilution of normal were timed for use as controls against the patient's unknown level. Both methods proved satisfactory. The viper venom method was more easily carried out because its control time is subject to very little variation even over long periods of time, whereas thromboplastin varies continuously and each batch must be tested daily. In order to develop standard technic and determine any factors that might alter the results, approximately 100 tests were carried out. It was interesting to find that determinations after breakfast were considerably higher in per cent prothrombin than those on fasting specimens. Prolonged application of the tourniquet or excessive trauma incident to prolonged attempts at venipuncture also raised the percentage reading toward normal. Only slight variations due to the personal factor were found among the technicians.

The exact therapeutic blood prothrombin level has still to be exactly determined. Some authors advise doubling the control time,⁴ others desire levels of 10 per cent to 30 per cent of normal,¹⁸ while the majority have found 20 per cent to 60 per cent levels to be both effective in preventing thrombosis and safe from the danger of hemorrhage. To accomplish this, fairly large initial doses of dicoumarol must be given, and to hold this lowered percentage, maintenance doses must be administered. It may be compared to digitalis therapy, for one "dicoumarolizes" the patient and then prescribes a daily maintenance dosage. The drug is prepared in the form of 50 or 100 mg. tablets or capsules and is for oral use only. Administration is begun only after a prothrombin test has been carried out and found to be in the region of normal.¹⁹

The initial dose used to induce hypoprothrombinemia has varied among those investigating its action, but most have used a schedule of a single dose of 300 mg. the first day, and 200 mg. the second day,^{20, 21, 22, 14} as was done in this study. It must be emphasized again at this time, that prior to these initial doses and all maintenance doses the plasma prothrombin level must be determined for that day. The single time this rule was disregarded was in a case of extensive thrombophlebitis of the deep veins of the leg and thigh. It was late in the day and rather than delay treatment for determination of the initial prothrombin level, 300 mg. of dicoumarol were prescribed. The next morning, the prothrombin percentage was 16, and it stayed near that level for 22 days. Excessive hypoprothrombinemia and hemorrhage are always potential dangers when the drug is "blindly" prescribed. From 24 to 72 hours are required to attain a therapeutic level of hypoprothrombinemia. After the second day, if the prothrombin time has not dropped satisfactorily, the 200 mg. dose of dicoumarol may be repeated daily until it does start to lower. At that point the dosage must be reduced in the manner later to be described. The lag period in reaching therapeutic prothrombin levels varies in each patient.²² In this series it was once felt that because most of these patients were large men, large initial dosages might drop the prothrombin percentage.

more rapidly. This was not entirely true, for doses as high as 600 mg. on two consecutive days required an average of 54 hours to reach a therapeutic level, while the 300 mg. and 200 mg. on consecutive days, a much safer dosage, required only six more hours.

In order properly to administer dicoumarol, the dosages and responses must be graphically recorded. The control times of normal and 10 per cent

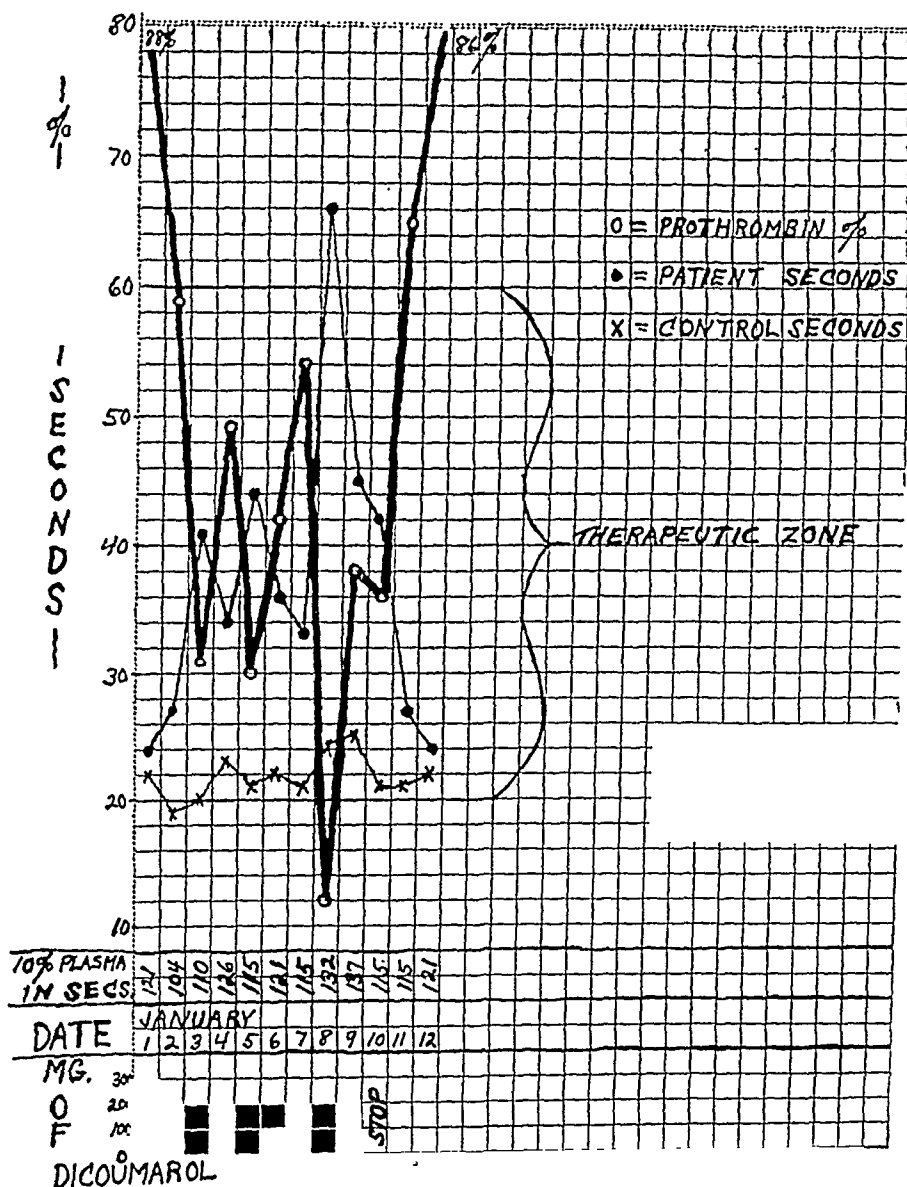


FIG. 1.

dilution of plasma, the patient's time, the patient's percentage prothrombin, and the dosages should be plotted daily as illustrated in figure 1. By thus recording these data, gross laboratory errors are evident, the response of the patient to each day's dosage is seen, and the trend of the curve with relation to the lag period and delay in effect of each dose is visualized.

The maintenance dosage for each day can be estimated from the responses and trend of the curves as plotted. If the percentage is in the upper part of the therapeutic zone, between 40 per cent and 60 per cent, and the curve is rising rapidly, a relatively heavy dose such as 200 mg. of dicoumarol is given. If it is rising rapidly in the lower zone, 20 per cent to 40 per cent, a smaller dosage, possibly 100 mg. would be prescribed. If the curve is almost horizontal in the lower therapeutic levels, 50 mg. or possibly none at all will be administered that day. In this series, the average daily dose of dicoumarol was 129.2 mg., but average dosage cannot be used as an index of treatment.²³ One must follow the graph and anticipate the effect today's dose is going to have on tomorrow's percentage. Only by following this trend and also the response of the patient to previous dosages, can the proper amount of dicoumarol be estimated for that day. In addition, deviations from the expected prothrombin times become conspicuous and allow one to recheck the laboratory and review the patient's status.

Upon discontinuing the administration of dicoumarol, there is a period of continued activity until the effect of the drug has worn off.^{22, 14} During this time, the prothrombin percentage gradually returns to normal. The average time for this to occur is 6.9 days, the shortest being one day and the longest 24 days.

The length of dicoumarol treatment varies with each case. Hypoprothrombinemia is induced as rapidly as possible. When it has been attained, further clotting ceases, and appropriate daily doses continue this inability to thrombose. With no new thromboses possible, the subsequent four or five days are sufficient time to allow all previously formed clots to become safely attached to the vessel wall. When this time has elapsed, the patient is started on gradually increasing exercise, if his primary condition permits. After several days of activity, the chances of thrombosis are remote, so the dicoumarol is stopped and the prothrombin level is allowed to rise.²⁴ In those cases in which the primary illness does not allow resumption of physical activity, the length of therapy must be judged accordingly. For example, one case in this series was a young soldier who developed bilateral ilio-femoral phlebitis that spread up the inferior epigastric veins as high as the costal margins. This came on while the patient had a paraplegia from a contusion of the spinal cord at D. 10. On dicoumarol the propagation ceased and all signs of phlebitis disappeared. It was felt that relatively soon he might regain muscular activity, for he could already move one toe. Dicoumarol was continued for two months, at which time he had fair motion of his toes, feet, and legs. The drug was then stopped, and he made a gradual uncomplicated recovery. In contrast to this case, another patient with paraplegia had a phlebitis of the deep veins of the calf and femoral vein of the right leg. He was placed on dicoumarol for only a two weeks period, for he was permanently paralyzed and the prophylactic use of dicoumarol would have meant lifetime administration, since he would never reach a stage where physical activity would normally prevent thrombosis. The average

number of days of hypoprothrombinemia was 15.5, the longest being 53 days, and the shortest four days. Patients have been reported as having had dicoumarol therapy for as long as three months.¹⁴ The average total dosage was 2004 mg., the largest was 6400 mg., and the smallest 800 mg. Liver and renal function tests, blood counts, and blood chemistry tests remained normal in all the cases investigated in this and other series.^{8, 10} The erythrocyte sedimentation rate tended to be elevated and the coagulation time prolonged.

Hemorrhage is the only toxic effect of dicoumarol. Excessive and uncontrolled dosage has led to fatalities.²⁵ In controlled therapy, hyper-reactors to the drug are encountered rather commonly. As high as 27 per cent of patients have been reported as hyper-reactors, but in this series only nine of the 60 patients (16.6 per cent) showed excessive response to ordinary dosage of dicoumarol. In four of these there was gross hematuria, in two, microscopic hematuria, and in three, no hemorrhagic phenomena at all. No other type of extravasation was observed, although others have reported purpura, oozing from wounds, ulcers, brain injuries or emboli, operative sites, and the gastrointestinal tract during excessive hypoprothrombinemia.^{8, 11, 12, 26} For this reason, daily physical examination and urinalysis are necessary for early detection of the hemorrhagic tendency.

Treatment of hemorrhage and excessively low prothrombin percentages involves restoration of the blood's ability to clot by replacing its deficient prothrombin. On this premise, transfusion of fresh whole blood was first used as the treatment, and was found effective. Since the amount of prothrombin transferred to the patient is proportional to the amount of blood given, several 400 c.c. transfusions may be needed to furnish enough prothrombin to overcome the deficiency. One or two transfusions are usually sufficient greatly to reduce the hemorrhage or cause it to cease completely. These may be repeated every few hours. Stored blood loses its prothrombin, and thus its beneficial action. This physiochemical action has been a useful factor in dicoumarol therapy when blood transfusion is required for the primary illness. Here the fresh blood of the donor would counteract the drug's action through its prothrombin content, but if the donor's blood is stored 24 hours, this action is minimized and tends not to disturb the prothrombin curve of the patient appreciably.

Another method of combating hemorrhage is the use of vitamin K (menadione bisulfite, hykinone), an essential substance for the formation of prothrombin.^{26, 27, 14} It is convenient and immediately available for use, being prepared in relatively inexpensive 10 c.c. ampules containing 60 mg. of the vitamin. This constitutes one therapeutic dose, and is massive when compared to the previously standard dose of 3.2 mg. which was ineffective and earlier had caused this drug to be considered useless in treating hypoprothrombinemia.^{26, 27, 28, 9, 18} It is given slowly intravenously and has shown no side reactions. It is used to have the body rapidly restore its blood prothrombin toward the normal level. This is not immediate, but

shows rise in two hours with maximum effect in eight hours.²⁰ When the quicker action of fresh blood is not urgently needed, this preparation may be used, especially in excessive hypoprothrombinemia without hemorrhage, or where hemorrhage is mild. It may be used also to fortify the action of blood transfusion. In this series, it was used at 12 hour intervals and was repeated twice if necessary. If more active treatment is needed, blood transfusion should be carried out as it was in one of these cases where, in spite of hykinone administration, hematuria persisted, and responded only to fresh blood. In all the other cases of hematuria, bleeding ceased or gradually subsided several hours after vitamin K therapy. In a case of hypoprothrombinemia without hemorrhage, hykinone and blood transfusion had little immediate effect, and it was not until six days later that the prothrombin spontaneously began to rise slowly. None of the cases of hematuria was serious or alarming, and all responded to therapy.

The contraindications for use of dicoumarol therapy are absolute and relative.²² The former are renal insufficiency, hepatic damage, bacterial endocarditis, purpura, bleeding tendencies, recent brain or cord injury. Relative contraindications are ulcers, open wounds, faulty absorption of vitamin K as in gastric, biliary, or bowel damage, and emaciation or severe nutritional deficiency.^{14, 29} The basis for these contraindications are obviously related to disturbance in prothrombin formation or the tendency for hemorrhage.

In 13 of the 56 cases of thrombophlebitis or phlebothrombosis, pulmonary embolism was the initial symptom. All were treated with dicoumarol and all recovered. Statistically, there should have been a 20 per cent mortality, had dicoumarol not been used.^{15, 22} These occurred during the most active days of combat, when 10,742 surgical procedures were carried out, while during the previous year, when dicoumarol was not used, there were four deaths from pulmonary embolism in a series of 2,604 surgical operations.

The thrombosis or phlebitis in these 56 cases ceased propagating in all but one in which for a few days a mild phlebitis in a few centimeters of superficial vein developed during very adequate therapy. In another four cases undergoing operation, which had recent severe phlebitis, dicoumarol was used prophylactically because of the high incidence of recurrence with subsequent operation. The drug was started the first or second day after operation in the usual manner, and effective prothrombin levels were reached the third or fourth postoperative day. No difficulties or complications were encountered, since care was taken to avoid hypoprothrombinemia too early postoperatively. None developed phlebitis or thrombosis. In a case on active therapy (prothrombin 30 per cent), suddenly requiring a major operation, 500 c.c. of blood were immediately given and repeated in four hours. At the time of operation, one hour later, the prothrombin percentage was 60 per cent. Bleeding was not excessive, and the postoperative course was uneventful.

The cases of phlebothrombosis and thrombophlebitis did exceptionally

well. Pain and edema seemed to be much milder on dicoumarol therapy,^{21, 19} and sympathetic blocks were done much less frequently than previously. The degree of chronic edema and residual symptoms also decreased considerably. The patients experienced no subjective discomfort or reaction, they all were comfortable and completely coöperative, and in a much healthier state of mind than those managed previously by surgical ligation of the veins, sympathetic blocks, and prolonged intravenous administration of heparin.

CONCLUSION

1. Dicoumarol is an effective anticoagulant.
2. The initial dosage of 300 mg. the first day, and 200 mg. the second day is the most suitable schedule for inducing hypoprothrombinemia.
3. Maintenance dosage is variable even in the same individual, and the daily plasma prothrombin time is the only index of the drug's action.
4. Hemorrhage is the only toxic action of dicoumarol. It can be controlled by fresh blood or vitamin K.
5. Absolute contraindications for use of dicoumarol are renal insufficiency, hepatic damage, bacterial endocarditis, purpura, bleeding tendencies, and recent brain or cord injury. Relative contraindications are ulcers, open wounds, faulty absorption of vitamin K as found in gastric, biliary, or bowel damage, and emaciation.

BIBLIOGRAPHY

1. DETAKATS, G., and FOWLER, E. F.: The problem of thrombo-embolism, *Surgery*, 1945, xvii, 153-157.
2. SMITH, L. A., and ALLEN, E. V.: Vascular clinics. XIV: Studies on the rate of venous blood flow: Physiologic studies and relation to postoperative venous thrombosis and pulmonary embolism, *Proc. Staff Meet. Mayo Clin.*, 1941, xvi, 53-56.
3. VEAL, J. R., and HUSSEY, H. H.: Surgery of deep venous thrombosis of the lower extremity, *Surgery*, 1945, xvii, 218-231.
4. REICH, C., YAHR, M. D., EGGERS, C., and LIPKIN, R.: Dicoumarol in the prevention of postoperative thrombosis and embolism, *Surgery*, 1945, xviii, 238-243.
5. HUNTER, W. C., KRYGIER, J. J., KENNEDY, J. C., and SNEEDEN, V. D.: Etiology and prevention of thrombosis of the deep leg veins, *Surgery*, 1945, xvii, 178-190.
6. EVANS, J. A.: Anticoagulation therapy of postoperative venous thrombosis and pulmonary embolism, *Surg. Clin. N. Am.*, 1944, xxiv, 534-537.
7. ALLEN, A. W., LINTON, R. R., and DONALDSON, G. A.: Thrombosis and embolism, *Ann. Surg.*, 1943, cxviii, 728-740.
8. BUTT, H. R., ALLEN, E. V., and BOLLMAN, J. L.: A preparation of spoiled sweet clover (3,3'-methylene-bis-(4-hydroxy coumarin)) which prolongs coagulation and prothrombin time of the blood: Preliminary report of experimental and clinical studies, *Proc. Staff Meet. Mayo Clin.*, 1941, xvi, 388-395.
9. WRIGHT, I. S., and PRANDONI, A.: The dicoumarin 3,3'-methylene-bis-(4-hydroxy-coumarin), *Jr. Am. Med. Assoc.*, 1942, cxx, 1015-1021.
10. BINGHAM, J. B., MEYER, O. O., and POHLE, F. J.: Studies on the hemorrhagic agent, 3,3'-methylene-bis-(4-hydroxycoumarin), *Am. Jr. Med. Sci.*, 1941, ccii, 563-578.
11. BOLLMAN, J. L., and PRESTON, F. W.: The effects of experimental administration of dicoumarin, *Jr. Am. Med. Assoc.*, 1942, cxx, 1021-1025.

12. RICHARDS, R. K., and CORTELL, R.: Studies on the anticoagulant 3,3'-methylene-bis-(4-hydroxycoumarin), *Proc. Soc. Exper. Biol. and Med.*, 1942, 1, 237-242.
13. DEBAKEY, M.: Dicoumarin and prophylactic anticoagulants in intravascular thrombosis, *Surgery*, 1943, xiii, 456-459.
14. BARKER, N. W., CROMER, H. E., HURN, M., and WAUGH, J. M.: The use of dicoumarol in prevention of postoperative thrombosis and embolism with special reference to dosage and safe administration, *Surgery*, 1945, xvii, 207-217.
15. BARKER, N. W., NYGAARD, K. K., WALTERS, W., and PRIESTLY, J. T.: A statistical study of postoperative venous thrombosis and pulmonary embolism. III. Time of occurrence during the postoperative period, *Proc. Staff Meet. Mayo Clin.*, 1941, xvi, 17-21.
16. QUICK, A. J., STANLEY-BROWN, M., and BANCROFT, F. W.: A study of the coagulation defect in hemophilia and jaundice, *Am. Jr. Med. Sci.*, 1935, cxc, 501-511.
17. PAGE, R. C., and RUSSELL, H. K.: Prothrombin estimation using Russel viper venom: simple modification of Quick's method, *Jr. Lab. and Clin. Med.*, 1941, xxvi, 1366-1370.
18. DAVIDSON, C. S., and MACDONALD, H.: A critical study of the action of 3,3'-methylene-bis-(4-hydroxycoumarin), *Am. Jr. Med. Sci.*, 1943, ccv, 24-33.
19. YAHR, M. D., REICH, C., and EGGER, C.: The treatment of thrombophlebitis, *Surg., Gynec. and Obst.*, 1945, lxxx, 615-619.
20. BUTSCH, W. L., and STEWART, J. D.: Clinical experiences with dicoumarin, *Jr. Am. Med. Assoc.*, 1942, cxx, 1025-1026.
21. ZUCKER, H. D.: Clinical experiences with dicoumarol, *Jr. Am. Med. Assoc.*, 1944, cxxiv, 217-220.
22. BARKER, N. W., ALLEN, E. V., and WAUGH, J. M.: The use of dicoumarol (3,3'-methylene-bis-(4-hydroxycoumarin)) in the prevention of postoperative thrombophlebitis and pulmonary embolism, *Proc. Staff Meet. Mayo Clin.*, 1943, xviii, 102-107.
23. WASSERMANN, L. R., and STATS, D.: Clinical observations on the effect of 3,3'-methylene-bis-(4-hydroxycoumarin), *Am. Jr. Med. Sci.*, 1943, ccvi, 466-474.
24. ALLEN, E. V., BARKER, N. W., and WAUGH, J. M.: A preparation from spoiled sweet clover, *Jr. Am. Med. Assoc.*, 1942, cxx, 1009-1015.
25. SKLEVIN, E. L., and LEDERER, M.: Uncontrollable hemorrhage after dicoumarol therapy with autopsy findings, *Ann. Int. Med.*, 1944, xxi, 332-341.
26. CROMER, H. E., and BARKER, N. W.: The effect of large doses of menadione bisulfite on excessive hypoprothrombinemia induced by dicoumarol, *Proc. Staff Meet. Mayo Clin.*, 1944, xix, 217-223.
27. SHAPIRO, S., REDISH, M. H., and CAMPBELL, H. A.: Prothrombin studies. III. Effect of vitamin K on hypoprothrombinemia induced by dicoumarol in man, *Proc. Soc. Exper. Biol. and Med.*, 1943, lii, 12-15.
28. OVERMAN, R. S., STAHLMAN, M. A., and LINK, K. P.: Studies on hemorrhagic sweet clover disease, VIII. The effect of 2-methyl-1,4-naphthaquinone and l-ascorbic acid upon the action of dicoumarol on the prothrombin time of rabbit, *Jr. Biol. Chem.*, 1942, cxlv, 155-162.
29. BARKER, N. W.: The use of dicoumarol in surgery, *Minnesota Med.*, 1944, xxvii, 102-106.

PENICILLIN AND SULFADIAZINE, COMPARED WITH SULFADIAZINE ALONE, IN THE TREATMENT OF PNEUMOCOCCIC PNEUMONIA *

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UNTIL the discovery of penicillin, sulfadiazine and several of its analogues were recognized universally as the drugs of choice in the treatment of pneumococcic pneumonia. When penicillin was shown to be active against pneumococci in vitro, the question of its relationship to the sulfonamides in the treatment of pneumococcic pneumonia became important. At first, since only small quantities of penicillin were available, this drug was reserved for patients who did not make the expected response to sulfonamides, but as the supply increased the problem of whether to treat all patients with penicillin from the start became paramount. In an attempt to solve this problem we decided to treat parallel groups of patients having typed pneumococcic pneumonia with sulfadiazine alone or with sulfadiazine plus penicillin.

PLAN OF THE STUDY

As soon as a patient was admitted to the medical wards of the Gallinger Municipal Hospital with the diagnosis of pneumonia, he was placed either in the group scheduled to receive 6 grams of sulfadiazine immediately, followed by 1 gram every four hours, or in the group which was to receive the same dose of sulfadiazine and penicillin in addition. Patients were assigned to one of these groups in strict alternation, from which there was no deviation, except that when a patient diagnosed on admission as having pneumonia was later found to have some other condition, such as pulmonary infarction or tuberculosis, his name was removed from the group to which it had been assigned and the name of the next patient admitted with the diagnosis of pneumonia was substituted for it.

In each group sulfadiazine was continued until the temperature had been within normal limits for about three or four days. Patients in the group treated with both sulfadiazine and penicillin received the first dose of each drug at the same time. The first three patients of this group were given 100,000 units of penicillin by continuous intramuscular drip by the method described by two of us¹ over a period of 12 hours. The next 14 patients received 200,000 units by the same route during the course of 24 hours. By this time penicillin had become more freely available, and it was decided to

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administer 15,000 units at two-hour intervals for 36 doses, making a total of 540,000 units in 72 hours of treatment. This schedule was adhered to for the remaining 76 patients, unless death intervened before the entire amount was given.

Four patients in the penicillin-sulfadiazine group were given additional penicillin after the termination of the scheduled regime, because they did not appear to be responding satisfactorily, or because of complications. All of these patients recovered. Two patients in the sulfadiazine series did not improve on sulfadiazine treatment and were given penicillin in addition nine and 12 days, respectively, after the sulfadiazine had been started. Both of these patients died.

Sputum for typing and blood for culture were collected on each patient before any treatment was given, and at suitable intervals thereafter. One or more roentgenograms of the chest were taken on each patient. Blood counts were made initially on each patient and frequently (usually every other day) thereafter, as long as the temperature remained elevated or sulfadiazine was being administered.

RESULTS

There were 94 patients with typed pneumococcic pneumonia in each group. Among those treated with sulfadiazine alone, nine patients (9.6 per cent) died, as compared with four (4.3 per cent) who died in the penicillin-sulfadiazine group. Two patients in the sulfadiazine group and one in the penicillin-sulfadiazine group died within 12 hours of the initiation of treatment. The two groups have been compared with respect to certain factors which are generally known to affect the prognosis in pneumonia,

TABLE I
Results of Treatment with Sulfadiazine, or Penicillin plus Sulfadiazine,
Arranged According to Type of Pneumococcus

Type	Sulfadiazine		Penicillin and Sulfadiazine	
	No. of Patients	Died	No. of Patients	Died
1	8	2	13	1
2	3	0	5	0
3	12	3	7	0
4	6	0	6	0
5	2	0	2	0
6	2	0	2	0
7	9	1	12	0
8	6	1	6	0
12	6	0	9	1
13	9	0	4	0
14	7	0	5	0
18	5	0	4	0
Other types	19	2	19	2
Total	94	9 (9.6%)	94	4 (4.3%)

namely, the type of the infecting pneumococcus, the age of the patient, the presence of associated diseases, and the incidence of bacteremia. As shown in table 1, the type distribution of pneumococci was approximately the same for the two groups.

When the ages of the patients in the two groups are compared (table 2) it is seen that there were more patients in the penicillin-sulfadiazine series under the age of 41 than there were in the sulfadiazine group. Nevertheless, there were no deaths in this age-period when the combined treatment was used, while there were three sulfadiazine-treated patients in the same age-period who died. In table 3 are listed the patients who had associated diseases. There were 12 of these in the sulfadiazine group, of whom four died, and 14 in the penicillin-sulfadiazine group, of whom one died.

TABLE II
Results of Treatment with Sulfadiazine, or Penicillin plus Sulfadiazine,
Arranged According to Age of the Patient

Age-Group	Sulfadiazine		Penicillin and Sulfadiazine	
	No. of Patients	Died †	No. of Patients	Died
12-20	8	0	5	0
21-30	17	1	24	0
31-40	22	2	27	0
41-50	19	0	27	2
51-60	16	2	5	0
61-70	3	1	3	1
71 and over	9	3	3	1
Total	94	9	94	4

Owing to the present shortage of technical personnel, it was necessary for blood cultures to be transported across the city to the Laboratory of the Health Department of the District of Columbia, where they were incubated and studied. Unfortunately, as a result of this, a great many of them became contaminated or failed to grow bacteria, so that only 11 patients were reported as having positive blood cultures, two in the sulfadiazine group and nine in the penicillin-sulfadiazine group. All of these patients recovered. Judging by our past experience in managing patients with pneumococcic pneumonia in the same hospital, and by the clinical appearance of the patients in the present series, we feel that another method of handling these cultures would have resulted in a much higher incidence of bacteremia.

From table 4, it will be noted that the complications were few and inconsequential in both groups with the exception of one patient in the penicillin-sulfadiazine group who developed empyema. He entered the hospital acutely ill with delirium tremens and pneumonia of an entire lung caused by the Type 33 pneumococcus. His temperature did not fall to normal in spite of treatment with sulfadiazine and penicillin. When the empyema was discovered several aspirations were made and then thoracotomy was done. He

TABLE III
Diseases Associated with the Pneumonia and Their Relation to Mortality

Diseases	Sulfadiazine		Penicillin and Sulfadiazine	
	No. of Patients	Died	No. of Patients	Died
Congestive heart failure	1	1	2	1
Auricular fibrillation	1	0	—	—
Auricular paroxysmal tachycardia	1	1	—	—
Acute alcoholism	3	0	6	0
Chronic bronchitis	2	0	1	0
Cirrhosis of liver	1	0	—	—
Bronchial asthma	1*	0	1	0
Carcinoma of stomach	1*	1	—	—
Pregnancy	—	—	1	0
Chronic glomerulonephritis	—	—	1	0
Subarachnoid hemorrhage	—	—	1	0
Pulmonary tuberculosis	1	1	—	—
Hemiplegia	—	—	1	0
Total	12	4	14	1

* Hypertensive heart disease also present.

TABLE IV
Complications of Pneumococcic Pneumonia in Patients Treated with Sulfadiazine or Penicillin plus Sulfadiazine

Complication	Sulfadiazine		Penicillin plus Sulfadiazine	
	No. of Patients	Died	No. of Patients	Died
Pleural effusion	—	—	3	0
Empyema	—	—	1	1
Delayed resolution	3	0	4	0
Spread into another lobe	1	0	—	—
Otitis media	1	0	1	0

improved for a while, but complete drainage was never established and he died 83 days after admission and 65 days after the thoracotomy. It is quite possible that the empyema was already present when this patient was admitted to the hospital, since he had been ill for eight days at that time and had received no treatment.

We have compared the two groups with respect to the time required for the temperature to fall permanently below 101° F., and found that they were strikingly similar in this respect. Such a drop in the temperature occurred within 24 hours in 47 patients in the sulfadiazine group and in 48 patients in the penicillin-sulfadiazine group.

No toxic effects were observed from the administration of penicillin. One patient developed drug fever, two dermatitis, and one gross hematuria from sulfadiazine. All of the patients received 6 grams of sodium bicarbonate with the initial dose of sulfadiazine and 3 grams with each subsequent dose.

COMMENT

As penicillin becomes more and more available, the physician is faced with the question of whether to treat all patients with pneumonia by the administration of one of the sulfonamides, reserving penicillin for use in case the response is not satisfactory, or to use penicillin, alone or in combination with a sulfonamide, from the very beginning. It seemed important to us to determine first of all whether the employment of penicillin offers any additional benefit over the use of sulfadiazine alone. In comparable groups of alternate patients treated with sulfadiazine alone and sulfadiazine plus penicillin, the lower case-fatality rate observed in the latter group, while not statistically significant, was highly suggestive. The results obtained in the two groups did not differ materially with regard to the rapidity of the fall in temperature or the presence of complications.

Studies such as the present one cannot be expected to do more than suggest the answer to the question as to the best method of treatment of pneumococcic pneumonia. In a series of cases, including those collected from the literature and those treated by one of us,² the death-rate from pneumococcic pneumonia was found to be as follows: among 1,616 patients receiving no specific treatment, 38.0 per cent; among 1,248 patients who were given specific antipneumococcic serum, 17.2 per cent; among 3,777 patients who received sulfonamides (with or without specific antiserum in addition) 13.5 per cent. From the data available at the present time, we have reason to expect the case-fatality rate to be lowered still further with the use of penicillin. Tillett and his associates³ and Bunn and his co-workers⁴ reported rates of 6.3 per cent and 2.2 per cent, respectively. Meads et al.⁵ used penicillin in the treatment of 54 severe cases of pneumococcic pneumonia with 10 deaths. Kinsman and his associates⁶ reported no deaths in a group of 75 soldiers treated with penicillin. The age and physical condition of these patients undoubtedly account for these excellent results, since there were likewise no deaths among 100 soldiers treated with sulfadiazine during the previous year at the same hospital.

Although the foregoing reports do not demonstrate conclusively that penicillin is superior to the sulfonamides in the treatment of pneumococcic pneumonia, nevertheless, when they are taken in conjunction with our results, they do suggest that this is true. By the time the number of patients who have been treated with penicillin approximates the number of those treated with the other effective agents, penicillin may have been found to be the most effective drug. Whether it should be used alone or in conjunction with the sulfonamides is a question which must be settled by further investigation.

In spite of the proper employment of the best therapeutic agents available, some patients with pneumococcic pneumonia will still die. In general, they are the patients in the older age-groups, those with complications, or those in whom treatment is initiated late because of delay in reporting to the phy-

sician or mistaken diagnosis. This is evident in the present group of patients treated with penicillin and sulfadiazine. Of the four patients who died, one was admitted in delirium tremens on the ninth day of the disease and died of empyema which may have been present before treatment was begun or may have developed during the treatment. Two were in the older age-groups, one being 80 years of age and the other 61. The latter also suffered from congestive heart failure and was a chronic alcoholic. The remaining patient was 42 years of age and was admitted in a moribund condition and died six hours after treatment was started. It is to such patients as these that our attention should be directed if we wish to lower the mortality rate still further.

It is worth noting that we did not encounter any instances of relapse or of secondary rise in fever in the patients treated with penicillin and sulfadiazine, even though the administration of penicillin was almost always discontinued 72 hours after treatment was begun. Such relapses have been reported³ in pneumonia patients treated for short periods of time with penicillin alone. Our good results were undoubtedly due to the fact that the sulfadiazine therapy was continued in every case until the temperature had been normal for two or more days. This fact might constitute a good argument for giving sulfonamides to patients with pneumonia along with penicillin, at least until penicillin becomes cheap enough so that its administration can be continued through two or more days of normal temperature.

SUMMARY AND CONCLUSIONS

1. Among 94 patients with typed pneumococcic pneumonia treated with a combination of penicillin and sulfadiazine, there were four (4.3 per cent) deaths, as compared with nine (9.6 per cent) deaths among a group of 94 patients treated in alternation with sulfadiazine alone.

2. There was no significant difference in the speed at which the temperature fell or in the development of complications of the pneumonia in the two groups.

3. The present study, taken together with the literature available at the present time, suggests that penicillin, when added to sulfadiazine for the treatment of pneumococcic pneumonia, is more effective than sulfadiazine alone.

The authors wish to thank Dr. George C. Ruhland, Dr. James G. Cumming, and Dr. John E. Noble for their coöperation, and Dr. J. B. Holland and Mrs. Rose Breen for technical assistance.

BIBLIOGRAPHY

1. HIRSH, H. L., and DOWLING, H. F.: Observations on the continuous intramuscular method of administering penicillin, *Am. Jr. Med. Sci.*, 1945, ccx, 435-443.
2. DOWLING, H. F.: Unpublished data.
3. TILLET, W. S., McCORMACK, J. E., and CAMBIER, M. J.: The treatment of lobar pneumonia with penicillin, *Jr. Clin. Invest.*, 1945, xxiv, 589-594.

4. BUNN, P. A., McDERMOTT, W., HADLEY, S. J., and CARTER, A. C.: The treatment of pneumococcic pneumonia with orally administered penicillin, *Jr. Am. Med. Assoc.*, 1945, cxxix, 320-327.
5. MEADS, M., HARRIS, H. W., and FINLAND, M.: Treatment of pneumococcal pneumonia with penicillin, *New England Jr. Med.*, 1945, ccxxxii, 747-755.
6. KINSMAN, J. M., DANIELS, W. B., COHEN, S., McCracken, J. P., D'ALONZO, C. A., MARTIN, S. P., and KIRBY, W. M. M.: The treatment of pneumonia with sulfonamides and penicillin, *Jr. Am. Med. Assoc.*, 1945, cxxviii, 1219-1224.

TREATMENT OF CARDIOVASCULAR SYPHILIS WITH PENICILLIN *

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Most authorities agree that specific therapy in cardiovascular syphilis favorably influences the course of the disease and increases life expectancy.¹ According to Scott² "any medication that tends to allay the process in the aorta and thus prevent its spread to the aortic orifice or retard the development of aneurysm, may add years to the patient's life." Moore and his associates,³ using preparatory heavy metals to avoid the possibility of Herxheimer reaction, followed by conservative arsenotherapy, have reported striking effects on the mortality rate and the average duration of life in this form of the disease.

The demonstration by Mahoney, Arnold and Harris,⁴ and others, that syphilitic lesions undergo rapid involution under penicillin therapy has suggested the use of this drug in the treatment of syphilis of the cardiovascular system. Wile,⁵ however, has warned of the likelihood of untoward reactions which might arise from the use of penicillin in this condition. Dolkart and Schwemlein⁶ have similarly stressed the danger of a therapeutic paradox in their recent report of two cases in which penicillin was thought to have induced untoward effects. In the first of their cases a single injection of 10,000 units of penicillin was administered on each of the first two days of treatment. On the third day, after the injection of 20,000 units of the drug, anginal attacks became more frequent and premature ventricular contractions were noted. In the second case, precordial pain developed after penicillin had been administered in the dosage of 20,000 units every two hours for a period of three days. In both instances the authors discontinued the use of the drug.

The experience of the writers with penicillin in relatively large dosage in 15 consecutive cases of syphilitic aortitis, including four cases of aortic aneurysm does not suggest any appreciable danger from this form of therapy. As shown in the accompanying table the dosage usually employed was 40,000 units every two hours for 85 doses. In one instance, Case 2, mild substernal pain recurred intermittently at rest on the third day of treatment but disappeared after several hours, without interruption of therapy. This patient showed the greatest subsequent improvement from treatment in the present

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TABLE I

Case	Age	History	Prev. Treatment	Lesion	Serology	Penicillin	Reactions	Remarks
1	48	Negative	None	Syphilitic aortitis	Maz. 4+ Kahn 4+	40,000 u. q. 2 hours— 85 doses	None	Spinal fluid Wasser- mann 4+
2	45	Chancre in 1925	None until 1944 then 25 inj. of As and Bi	Double aortic aneurysm	Maz. + Kahn-neg.	40,000 u. q. 2 hours— 85 doses	Mild sub- sternal pain on 3rd day of treatment	Marked clinical improve- ment
3	52	Negative	None	Aortic aneurysm	Maz. 4+ Kahn 4+	40,000 u. q. 2 hours— 85 doses	None	Improved
4	42	Chancre in 1935	16 As and 16 Bi inj. in 1935	Aortic aneurysm	Maz. 1+ Kahn 3+	40,000 u. q. 2 hours— 85 doses	None	
5	40	Chancre in 1930	None until 1943 then 15 As and 2 Bi injec- tions	Syphilitic aortitis	Maz. 4+ Kahn 4+	40,000 u. q. 2 hours— 85 doses	None	Marked clinical improve- ment
6	59	Negative	None	Syphilitic aortitis	Maz. 4+ Kahn 4+	40,000 u. q. 2 hours— 85 doses	None	
7	45	None	None	Syphilitic aortitis	Maz. 4+ Kahn 4+	40,000 u. q. 2 hours— 85 doses	None	
8	52	Negative	None	Syphilitic aortitis	Maz. 4+ Kahn 4+	60,000 u. q. 2 hours— 85 doses	None	Spinal fluid Wasser- mann 4+
9	51	Negative	None	Syphilitic aortitis	Maz. 4+ Kahn 4+	20,000 u. q. 2 hours— 85 doses	None	
10	35	Chancre in 1940	Inadequate treat.— 1940-1944	Syphilitic aortitis	Maz. 3+ Kahn 2+	40,000 u. q. 2 hours— 85 doses	None	
11	40	Chancre in 1930	None until 1944— then alter. courses As and Bi	Syphilitic aortitis	Maz. 4+ Kahn 4+	40,000 u. q. 3 hours— 125 doses	None	
12	57	Chancre in 1929	Inadequate treat.— 1931	Syphilitic aortitis	Maz. 4+ Kahn 4+	40,000 u. q. 2 hours— 85 doses	None	Improved
13	40	None	Inadequate treatment	Aortic aneurysm	Maz. 4+ Kahn 4+	40,000 u. q. 2 hours— 85 doses	None	
14	46	Chancre in 1932	Inadequate treatment in 1940	Syphilitic aortitis	Maz. 3+ Kahn 2+	40,000 u. q. 2 hours— 85 doses	None	
15	48	None	None	Syphilitic aortitis	Maz. 4+ Kahn 4+	40,000 u. q. 2 hours— 85 doses	None	

series. Substernal pain on effort, which was manifested even after a control period of prolonged bed rest, almost completely abated following the course of penicillin. Three other cases similarly appeared to manifest significant increments in coronary reserve after treatment. However, electrocardiographic confirmation of such improvement was not obtained. As was anticipated, no noteworthy change in serologic reactions was observed in the follow-up period, which varied from one to three months.

From these observations it would appear that significant untoward reactions from penicillin are uncommon in cardiovascular syphilis. That this similarly applies to other forms of late and latent syphilis is indicated by the failure to encounter a single instance of therapeutic paradox in 389 cases of central nervous system and latent syphilis treated with penicillin on the Venereal Disease Service of the U. S. Marine Hospital in Staten Island. These findings are in striking contrast with the frequency of Herxheimer reactions noted in similarly treated cases of early syphilis in which the incidence approximated 90 per cent. It is possible, moreover, that such reactions as do occur in patients suffering from cardiovascular syphilis may not necessarily warrant discontinuance of therapy. Further observations may indicate that the success of this form of treatment justifies the risk entailed.

SUMMARY AND CONCLUSIONS

Fifteen consecutive cases of cardiovascular syphilis, including four with aortic aneurysm, were treated with penicillin in the dosage of 40,000 units every two hours for 85 doses. No significant untoward reactions necessitating discontinuance of the drug were encountered. Four patients showed distinct improvement in coronary reserve following treatment. It is concluded that harmful reactions to penicillin are uncommon in cardiovascular syphilis during the treatment and early post-treatment periods and that this form of therapy warrants further evaluation.

BIBLIOGRAPHY

1. WHITE, P. D.: Heart disease, 1944, ed. 3, The MacMillan Company, New York, p. 385.
2. SCOTT, R. W.: in Oxford Medicine, The Oxford University Press, New York, 1942, p. 508.
3. MOORE, J. E., DANGLADES, J. H., and REISINGER, J. C.: Treatment of cardiovascular syphilis: Results obtained in fifty-three patients with aortic aneurysm and in 112 with aortic regurgitation, Arch. Int. Med., 1932, xlix, 879.
4. PADGET, P., and MOORE, J. E.: The results of treatment in cardiovascular syphilis: A report of three years' additional observation, Am. Heart Jr., 1935, x, 1017.
5. MAHONEY, J. F., ARNOLD, D. C., and HARRIS, A.: Penicillin treatment of early syphilis: A preliminary report, Ven. Dis. Inform., 1943, xxiv, 355.
6. WILE, U. J.: News from the centers, Bull. Rapid Treatment Centers, 1945, ii, 12.
6. DOLKART, R. E., and SCHWEMLEIN, G. X.: The treatment of cardiovascular syphilis with penicillin, Jr. Am. Med. Assoc., 1945, cxxix, 515.

CASE REPORTS

GENERALIZED XANTHOMATOSIS WITH PULMONARY, SKELETAL AND CEREBRAL MANIFESTATIONS: REPORT OF A CASE*

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IN recent literature there have appeared numerous case reports of lipoid granulomatosis or xanthomatosis with its varied clinical manifestations. Typical Hand-Schüller-Christian disease with its triad of symptoms, consisting of defects in membranous bones, exophthalmos and diabetes insipidus, is now considered as the craniohypophyseal localization of lipoid granulomatosis.¹ On the basis of pathological studies, Green and Farber² have concluded that eosinophilic or solitary granuloma of bone is one form of generalized xanthomatosis and not a new disease entity. These authors also describe Letterer-Siwe disease or reticulo-endotheliosis as the same pathological process seen in Hand-Schüller-Christian disease. Wherever there is reticulo-endothelium there can be lipoid granulomatosis. Thus, the clinical symptoms produced depend upon the tissues involved and the degree of involvement. The following case is one with pulmonary, skeletal and cerebral involvement.

CASE REPORT

P. V. G., a white man, aged 35, was admitted to the Los Angeles County General Hospital on November 27, 1942 with the complaint of increasing shortness of breath of three days' duration.

The past medical, familial and marital histories were irrelevant. The patient stated that at the age of 20 years many of his teeth became loose and began to fall out. A diagnosis of "trench mouth" was made, following which all of his remaining teeth were removed. In 1933 he awoke one morning extremely thirsty, requiring large amounts of water, which failed to satisfy him. Frequency of urination and excessive amounts of urine were noted simultaneously. At this same time he had pains in the left lumbar region and the upper right thigh. The pains were intermittent and resulted in weakness of the right leg. There had been no previous history of trauma. In July 1934 he experienced a sharp pain in the left chest after throwing a rock. This pain became more severe and was accompanied by shortness of breath. With these symptoms he was seen in the Oklahoma University Hospital out-patient clinic, where a roentgen-ray diagnosis of left pneumothorax and pulmonary tuberculosis was made. He was admitted to a sanatorium, where, after two weeks, his symptoms disappeared and he was told that he did not have tuberculosis.

In October 1934 he entered the Oklahoma University Hospital because of excessive thirst and urination, which had continued since 1933. Aquamedrin, intermedrin and obstetrical pituitrin caused a moderate reduction in intake and output of

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From the University of Southern California Medical School and the Los Angeles County General Hospital; aided by the Michael J. Connell Charities, Ltd.

fluid. Roentgenograms revealed normal skull series and generalized fibrosis of lungs. The impression at that time was old fibrous tuberculosis, although multiple small cysts were not ruled out. He was discharged after one month, only to be readmitted three weeks later, complaining of pain in his left chest and shortness of breath, which appeared after a paroxysm of coughing, induced by "flu". Almost complete collapse of the left lung was found. No specific therapy was given for the pulmonary lesions, but the previous treatment for diabetes insipidus was successfully resumed.

In 1938 he made an uneventful recovery from an automobile accident resulting in fractured right ribs and lacerations of the head.

In June 1939 he was again admitted to the Oklahoma University Hospital complaining of pain in his back and legs, excess thirst and frequency of urination. Roent-



FIG. 1. November 27, 1942. Bilateral pneumothorax and marked fibrosis of lungs.

genograms revealed large cystic areas with well defined borders involving both iliac bones, the right ischium and pubic bone and the neck and trochanteric areas of both femora. An area of destruction involving the anterior portion of the body of the first lumbar vertebra was also noted. A diagnosis of osteitis fibrosa cystica was made. Again he was put on obstetrical pituitrin daily, with marked response. He was discharged in two weeks, being advised to inject $\frac{1}{2}$ c.c. of pituitrin daily.

His final admission to the Oklahoma University Hospital was in May 1940 with similar complaints of thirst and excessive urination. He had been unable to afford pituitrin. He also complained of marked weakness of his legs and was forced to use crutches for walking. Marked muscular atrophy was observed, being more marked in the lower extremities. Slight flexion contractures of the thighs and knees were

present. A slight left scoliosis in the lower dorsal area with abnormal prominence and tenderness of the twelfth dorsal vertebra was noted. Upper extremity reflexes were hyperactive. Fluid intake and output averaged five to six liters per 24 hours at this time. Roentgenograms were found the same as in 1939 except for a healed pathological fracture of the right femur.

The patient was admitted to the Los Angeles County General Hospital November 27, 1942. Seven days previously he had developed a cough which he attributed to excessive smoking. He had noticed pain in the left chest when he tried to lie on his left side. Three days later the right side of his chest had become painful also. This was followed by sudden onset of shortness of breath. Owing to progression of symptoms, he came to the hospital.



FIG. 2. January 12, 1943. Numerous large and small cystic areas in pelvis and femora.

Physical examination revealed a poorly developed and poorly nourished male who appeared older than his age. He was in severe respiratory distress, and his lips and nail beds were moderately cyanotic. Temperature was normal and pulse rate was 125. Respirations were 38 and blood pressure was 120 mm. Hg systolic and 80 mm. diastolic. The mouth was edentulous. The chest revealed no lag and equal expansion bilaterally. Tactile fremitus was markedly diminished bilaterally. The lungs were hyperresonant. Breath and voice sounds were markedly diminished except in a small area between the scapulae. Cardiac dullness was absent and the heart sounds were faint. Slight left dorsolumbar scoliosis and kyphosis were noted. Generalized weakness and atrophy were present in the lower extremities. The patient could not walk without the aid of crutches.

Roentgenograms of the chest revealed the right lung to be approximately 60 per cent expanded and the left lung approximately 70 per cent (figure 1). On the

right, there were several adhesions in the second interspace anteriorly, and on the left the pleura was bound down by adhesions in the entire apical and subapical areas. Both leaves of the diaphragm were flattened and markedly depressed. The parenchymal tissue of both lungs showed marked accentuation of the reticular pattern with several emphysematous blebs.

Because of the severe dyspnea, oxygen inhalations were started immediately. This was followed by numerous aspirations of air from both pleural cavities over a period of 12 days. Finally a water trap suction was used for half a day with marked symptomatic improvement. The patient was discharged after one month, having been asymptomatic for about two weeks. Roentgenograms taken upon discharge

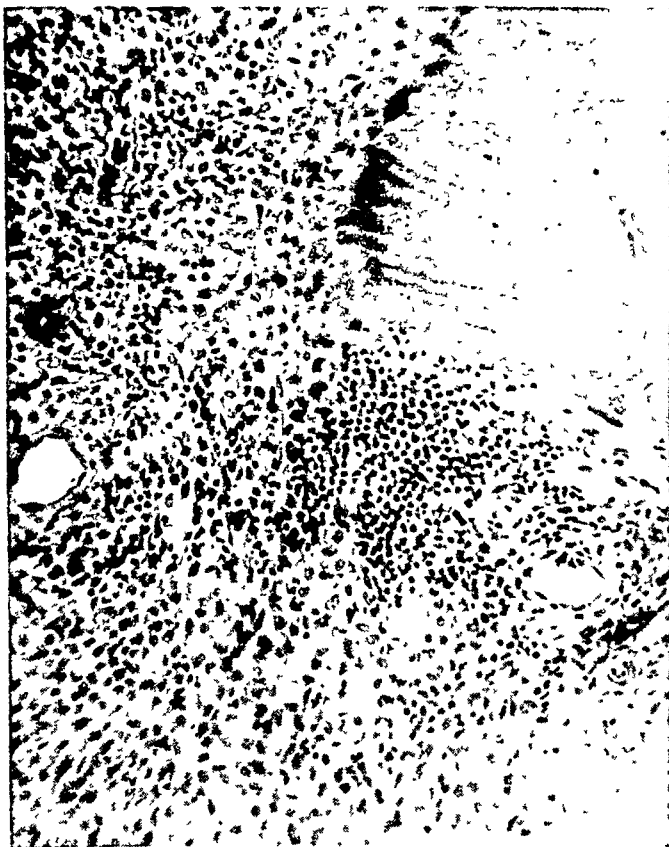


FIG. 3. February 6, 1943. Photomicrograph of a section from a lesion in the right ilium. Numerous eosinophiles and large macrophages with foamy cytoplasm are seen. (Hematoxylin and eosin stain. Magnification 250 diameters.)

showed the left lung completely expanded and the right lung approximately 70 per cent expanded.

The patient was seen in the out-patient department January 11, 1943, still using crutches to walk. He complained of respiratory difficulty, though a roentgenogram revealed the right lung to be approximately 50 per cent expanded. Roentgenograms of the pelvis and femora revealed large cystic areas in both iliac crests and above the acetabula (figure 2). The borders of these cystic areas were sclerotic in most instances. Similar cystic areas were present in the trochanteric and subtrochanteric areas of the femora. There was moderate atrophy of the shafts of the femora, consistent with disuse. The lumbar spine revealed a wedging and narrowing of the first lumbar vertebra with a large destructive lesion in the ventral portion of the body.

There was a left-sided scoliosis, with the apex between the first and second lumbar vertebrae.

The patient was readmitted to the Los Angeles County General Hospital on February 1, 1943 for more complete examination and study. At that time there were no complaints except for an occasional dull aching pain in the right thigh. He was drinking two gallons of water daily, which was not as much as in the past. His physical examination was essentially the same as on the previous admission except for absence of pneumothorax.

Laboratory findings revealed water-clear urine with a specific gravity of 1.002. No albumin or sugar was found and the microscopic examination was essentially

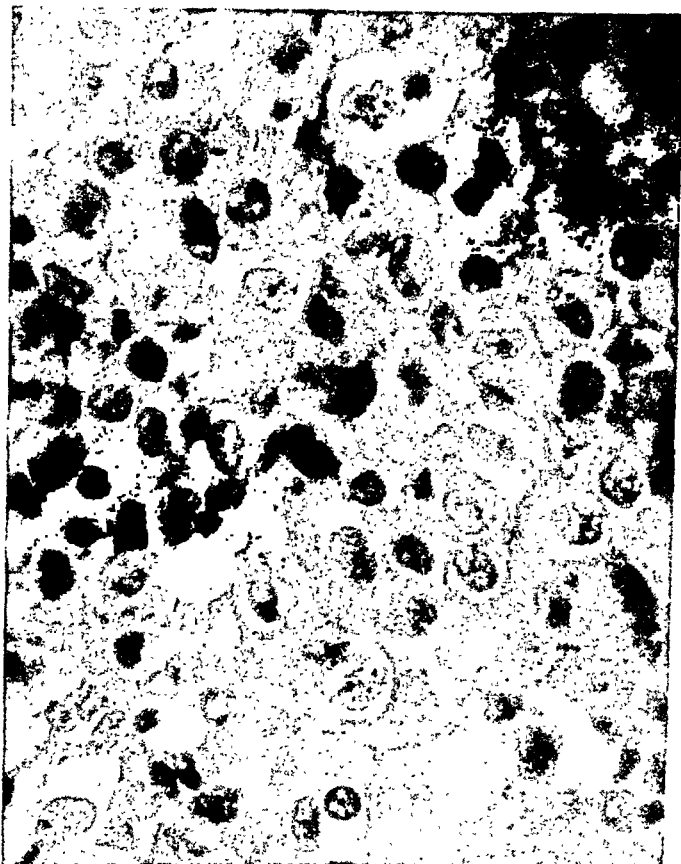


FIG. 4. February 6, 1943. Photomicrograph from the same section showing characteristic foamy cells with sharp cell borders. (Hematoxylin and eosin stain. Magnification 500 diameters.)

negative. The urinary output varied between 6 to 10 liters per 24 hours. The Mosenthal test revealed urinary concentration to a specific gravity of 1.005 in nine hours with a loss of seven pounds in weight. Four liters of urine were excreted. At this time the patient became very uncomfortable and demanded fluids. Hemoglobin, blood count and differential were normal.

Numerous blood chemistry determinations were done at the Oklahoma University Hospital beginning in 1934 and continuing through 1940, all of which were within normal limits except for the glucose tolerance tests. Similar results have been reported in the Los Angeles County General Hospital. The concentrations of various substances tested for in milligrams per 100 cubic centimeters of serum are as follows, with these figures representing averages of several tests and the number of tests

appearing in parentheses: Calcium (5) 9.6; phosphorus (3) 3.6; uric acid (1) 3.5; cholesterol (4) 195; cholesterol esters (4) 67.3. A single non-protein nitrogen determination revealed 35 milligrams per 100 cubic centimeters of whole blood. The average of three alkaline phosphatase determinations was 3.76 Bodansky units, while a single acid phosphatase determination revealed 2.1 Bodansky units. The serum albumin was 4.7 grams and the serum globulin 2.6 grams per 100 cubic centimeters of serum. The five-hour oral glucose tolerance tests revealed the following results: 82.9, 99.5, 63.3, 68.5, 73.5 mg.; 80, 133, 121, 46, 59, 76 mg.; 84, 148, 125, 98, 84 mg. per 100 cubic centimeters of whole blood. Repeated Wassermann and Kahn tests were negative. A 24 hour excretion of 6 liters of urine contained 528 mg. of calcium.



Fig. 5. February 6, 1943. Photomicrograph from the same section reveals fat droplets throughout the foam cells. (Osmic acid stain. Magnification 500 diameters.)

On February 6, 1943 a biopsy was taken from the right ilium under a general anesthetic. Grossly, the cystic area explored was filled with grayish-yellow, fibrous tissue. The bone bordering the cyst was more dense than the surrounding bone. There was no abnormal bleeding about this particular cystic area. Microscopic examination revealed a granulomatous process with reticulum-type cells present in both large and small groups. Many of these cells were foamy in appearance with rather sharp cell borders. Large numbers of eosinophiles were seen scattered throughout. Fat stain (osmic acid) revealed many fat droplets within the foam cells (figures 3, 4 and 5). Smears and cultures of the specimen removed at biopsy revealed no aerobic or anaerobic bacteria.

Following operation, the patient was started on 1 c.c. of surgical pituitrin, following which there was slight gain in weight but very little improvement of his urinary

output. Two weeks later posterior pituitary powder was given in 2 grain doses three times a day by nasal insufflation. For the first time in 10 years his fluid intake and output decreased markedly, approaching normal quantities. On the same day pituitary powder was begun, he was started on a course of roentgen-ray therapy over the pelvic bones. Through each of five portals the patient received, in divided doses, 400 roentgen units in air. The technical factors were 200 KV, 20 MA, Cu 0.5, Al 2.0, T.S.D. 50 cm., (H. V. L. 1.0 Cu).

After about one month's stay in the hospital the patient was discharged to the outpatient department. He improved symptomatically and was able to walk without the aid of crutches.



FIG. 6. May 17, 1943. Pathological fracture through cystic areas of right femur after five weeks in traction. Abundant callus present.

On April 12, 1943 he fell, incurring pain in the right thigh and hip. Reentry into the hospital at that time revealed characteristic signs and symptoms of a subtrochanteric fracture of the right hip. Roentgenograms revealed a pathological fracture through cystic areas in the subtrochanteric region. Russell traction was applied immediately after admission. After two months in traction, roentgenograms revealed good position of the fracture and adequate callus (figure 6). Traction was removed and the patient was discharged.

Repeated roentgenograms taken during the following year and a half showed no significant change in the bony lesions about the spine and pelvis. Films of the chest revealed almost complete disappearance of the pneumothorax except for a small area

in the right costophrenic sulcus (figure 7). During this interval the patient was able to control his diabetes insipidus with pituitary powder. There had been one episode of coughing with slight hemoptysis and chest pain but without evidence of pneumothorax on physical examination. Except for occasional slight pain in the right hip, he had had no symptoms referable to his healed fracture.

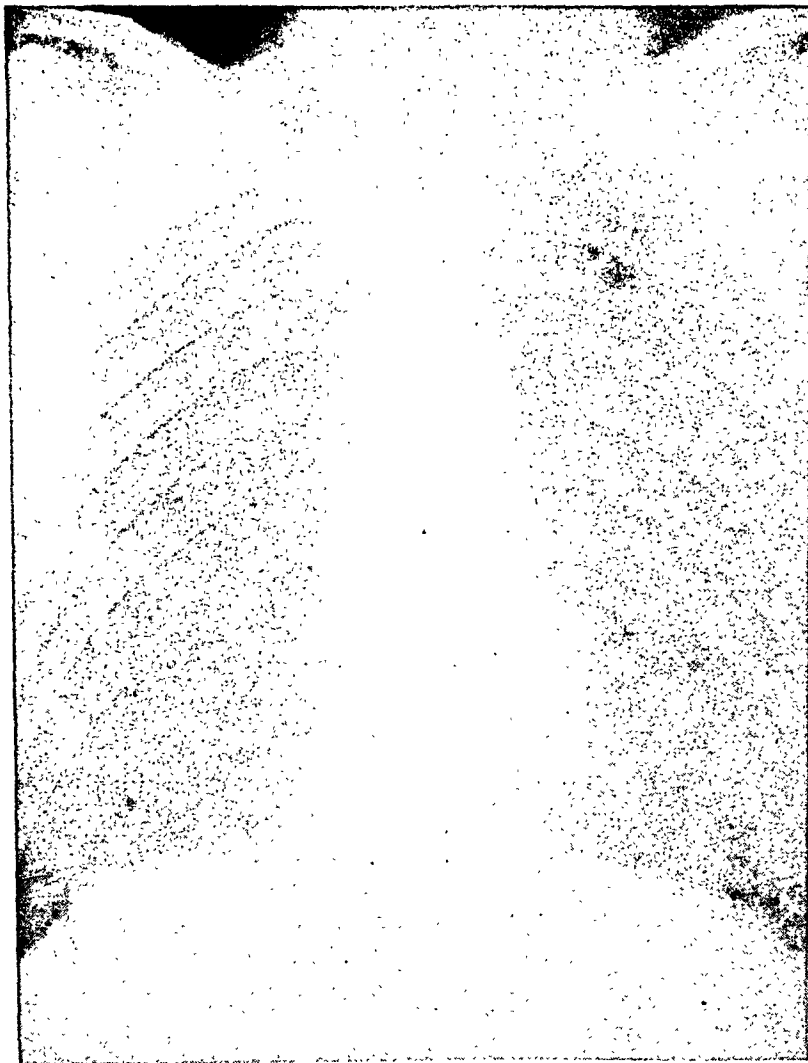


FIG. 7. May 28, 1943. Nearly complete disappearance of pneumothorax. Extensive fibrosis is present.

COMMENT

The case reported illustrates some of the protean manifestations which may occur in generalized xanthomatosis. The definitive diagnosis was made by biopsy of a bone lesion. There was extreme pulmonary involvement with fibrosis and resulting bilateral pneumothorax. It was this condition which forced the patient to seek hospital care. After pleural aspirations the lungs remained expanded for a year and a half without further treatment. Because of advanced fibrosis within the lungs, roentgen therapy to these areas was deemed inadvisable.

Apparent hypophyseal involvement produced diabetes insipidus which was well controlled by the use of posterior pituitary powder.

Bone lesions were limited to vertebrae, pelvis and upper portions of the femora. The pelvic lesions did not alter in size following roentgen therapy. A pathological fracture occurred through the lesions in the right femur. This healed with conservative treatment and without unusual delay.

SUMMARY

A case of generalized xanthomatosis with involvement of bone, lungs and cerebrum has been presented. The unusual complication of bilateral spontaneous pneumothorax occurred in this case.

BIBLIOGRAPHY

1. SNAPPER, I.: Medical clinics on bone diseases, 1943, Interscience Publishers Inc., New York, p. 151.
2. GREEN, W. T., and FARBER, S.: "Eosinophilic or solitary granuloma" of bone, Jr. Bone and Joint Surg., 1942, xxiv, 499.

ALLERGY IN MALARIA *

By HARVEY F. GRAZIER, Captain, MC, AUS, *Johnstown, Pennsylvania*

THE various manifestations of malarial infection are common knowledge, but specific sensitivity to the protein of the malarial parasite is almost a medical curiosity. References to such a condition in the available literature are very few, and detailed case reports almost non-existent. The relationship between urticaria and malarial infection has been infrequently observed over the past 25 years, but as late as 1939 the possibility of urticaria existing coincidentally with and not related to malarial infection was under discussion. In 1928 Thonnard-Neumann described cases in Haiti in which treatment of malaria cured coexistent asthma. More recently urticaria as a result of specific sensitivity to the malarial parasite has been shown in cases reported by Gouriou in 1938, Chatterjee in 1939, Sen Gupta in 1942, and others.

The case reported below was intimately observed by the writer, resulting, in contrast to previous reports of this condition, in considerable available detail.

CASE REPORT

A 26-year old white male in excellent health entered the Solomon Island area in the summer of 1943. He immediately began to take suppressive atabrine. On August 27, 1943 the patient developed generalized urticaria manifested by small wheals over the entire body. This persisted about two hours and disappeared without treatment. Suppressives atabrine was continued. On September 30, 1943 the patient developed angioneurotic edema of both lips with concomitant swelling of the forehead and eyelids and again the generalized urticaria previously noted. This episode occurred about mid-day and was controlled with adrenalin 1:1000 in 0.5 c.c. doses at hourly intervals.

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Because he felt slight chilliness, his temperature was taken, found to be 102° F. and was thought to be due to the adrenalin. The following day the patient felt perfectly well, and no sign of allergy was noted. About mid-day October 2, 1943, 48 hours after the initial attack, the patient again developed angioneurotic edema and generalized urticaria as described above. The attack was controlled in similar manner, and again the chilliness and fever of 102.2° F. were noted. In the late afternoon the patient complained of severe frontal headache, mild backache and general malaise. A clinical diagnosis of malaria was made and routine atabrine therapy instituted. Thick and thin blood smears taken on the mornings of October 3 and October 4 (after 9 grains of atabrine) were negative for malarial parasites. The course of atabrine was completed within seven days, and no recurrence of allergic manifestations or signs and symptoms of malaria occurred. Suppressive atabrine was continued. The patient was in excellent health until November 11, 1943 when about mid-day of that date without warning he developed angioneurotic edema with swelling of the forehead, eyelids, lips and generalized urticaria. This was controlled with adrenalin 1:1000 given in 0.5 c.c. subcutaneous injections at half-hourly intervals and then at hourly intervals over a period of four hours for a total dosage of 3 c.c. Because of previous experiences and not because of any chilliness or malaise the temperature was taken and found to be 101.2° F. The following day the patient felt well and nothing unusual occurred. On November 13, 1943 there was an exact duplication of the allergic manifestations which had occurred 48 hours previously, and this was controlled in similar manner though more adrenalin was necessary. However, following subsidence of the urticaria the patient had a slight headache and slight malaise. Temperature at this time was 102.2° F. On November 14, 1943 about mid-day the patient suddenly developed edema of the lower lip followed rapidly by hoarseness, aphonia and finally dyspnea. One c.c. 1:1000 adrenalin was immediately administered with relief of the dyspnea and aphonia, but the hoarseness persisted. The patient was taken to a field hospital where a laryngoscopic examination was made and edema of both vocal cords seen. On this date there was no generalized urticaria, and the malaise and headache of the day before were now replaced by considerable apprehension. The temperature was not taken. Patient was admitted to the field hospital for evacuation by air to a rear area for further study; he was to leave the following day. In the forenoon of November 15 while sitting on the side of his bed awaiting the arrival of transportation to the plane, the patient sensed the generalized pruritus which presaged the onset of the urticaria and angioneurotic edema. He arose in an attempt to obtain the syringe containing adrenalin but collapsed on the floor of the ward tent in syncope. The male nurse immediately administered 1 c.c. of adrenalin subcutaneously. The patient regained consciousness after a very few seconds and complained of chilliness. Examination at the time revealed extreme pallor and a rapid, thready pulse. Within a few minutes a typical severe shaking chill developed and persisted for about a half hour. Two and a half hours from the time of administration of adrenalin the temperature was found to be 104.6° F. Blood smear for malarial parasites at this time revealed numerous *P. vivax* and combination quinine-atabrine therapy was immediately begun. The patient was evacuated on a stretcher by air three hours later to a station hospital in a rear area.

Family history: Father died at age 43 of pulmonary tuberculosis. Mother, living and well, aged 64. One brother and one sister living and well. History of migraine in the mother, sister, and brother. Sister in past suffered occasional attacks of hives, allergen unknown.

Past history: Usual childhood diseases. Patient has suffered attacks of typical migraine since puberty, approximately four per year. All types of treatment have been tried without success, including an elimination diet.

Patient can recall no previous attacks of hives or other allergic phenomena herein described.

Physical examination at the time of entry into the station hospital: The patient was a fairly well developed white male, age 26, decidedly apprehensive. The sclerae were clear. The nose and throat were normal. The heart showed no abnormality. Blood pressure was 100 mm. Hg systolic and 68 mm. diastolic. No abnormal signs were elicited in the chest. There was an enlarged, tender spleen. The skin was clear.

Clinical course in the station hospital: Anti-malarial therapy was continued as instituted in the field hospital. Difficulty in retaining the medication by mouth was encountered because of severe nausea and vomiting. During the night of November 18 the temperature slowly rose from 100° F. at 1800 to 105.8° at 0400 the morning of November 19. Morphine sulfate was administered and intravenous fluids were begun. Temperature ranged between 101° and 104° through November 19 and fell by lysis on November 21. Nausea and vomiting ceased on November 21, the appetite slowly returned and the condition steadily improved. Anti-malarial therapy was continued in the form of quinine and atabrine for 12 days and atabrine for an additional six days, a total of 18 days. At the time of discharge from this hospital the patient had lost 31 lb. in weight.

Laboratory studies: November 16, 1943. Blood smear showed *P. vivax*.

November 19, 1943. Urinalysis: albumin 2 plus, red blood cells 3 to 6 and white cells 2 to 4 per high power field. Blood: Red cells 4,500,000; white cells 6,000. Differential: polymorphonuclears 66 per cent, lymphocytes 32 per cent, monocytes 2 per cent. Sedimentation rate 26 mm. per hour. Icterus index, 4.

November 20, 1943. Urinalysis: albumin negative. Microscopic negative.

November 24, 1943. Blood: Red cells 3,700,000; white cells 4,700. Differential: polymorphonuclears 54 per cent, lymphocytes 42 per cent, monocytes 2 per cent, eosinophiles 2 per cent.

Subsequent course: Patient returned to the United States and was hospitalized in a general hospital. Weight gain was satisfactory, and there was no recurrence of allergic phenomena or symptoms of malaria. He was discharged to duty March 3, 1944. On March 23, 1944, about mid-day, there occurred the familiar onset of generalized urticaria which was controlled in the manner previously described. Following administration of adrenalin, the temperature rose to 102.4° F. Because the patient was at home on leave no laboratory examinations were made but a complete course of atabrine therapy was taken. There was no further episode of allergy following the initial dose of atabrine. Patient was then in excellent health, doing full duty, until September 6, 1944 when generalized severe urticaria recurred. This was controlled as usual by adrenalin, and the temperature rose to 101.8°. Blood smear taken at this time was negative for malarial parasites but despite this a complete course of atabrine was taken. Patient was entirely well and free from allergic manifestations until October 23, 1944 when again he experienced the sudden onset of generalized urticaria. The urticaria persisted for 12 hours during which time 14 0.5 c.c. subcutaneous injections of 1:1000 adrenalin were required to control the symptoms. On this occasion a new feature was noted: namely, sudden swelling and severe pain in the metacarpophalangeal joints of both hands. Combined quinine and atabrine therapy was immediately instituted with no further recurrence of either the urticaria or malaria to date, an interval of six and one-half months.

COMMENT

The last three recurrences of urticaria and malaria in this case were not proved by positive blood smear. The explanation is that the sensitivity of this patient to the malarial parasite was presumably so great as to result in allergic phenomena 48 hours before the first subjective clinical symptoms of malaria alone

would have appeared and that on the basis of previous experiences, atabrine was instituted 48 hours early thus aborting the usual paroxysm and clinical symptoms such as chills, fever and malaise.

DISCUSSION

In the few described cases of this rare condition, the allergic phenomena invariably accompanied or appeared immediately preceding the fever. The similarity of the sequence of events in the many recurrences of the individual cases conclusively points out the relationship between the malaria and the allergic phenomena. The fact that the latter disappeared on institution of quinine or atabrine therapy equally well rules out the possibility that any quinine or atabrine idiosyncrasy might be responsible for them.

Pathogenesis of the condition is not clear. It has appeared in the presence of both benign tertian and malignant tertian types of infection. The allergic reaction occurs at a time when merozoites are free in the blood stream, thus foreign protein is available to cause an allergic reaction. Probably allergic phenomena are not encountered more frequently in malaria, because of the rarity of the specific sensitivity or susceptibility of the host. The writer has seen approximately 500 cases of malaria with but one instance of specific sensitivity to the malarial parasite. It is apparent that the incidence of the condition is much less than this but no exact figures are available at this time.

BIBLIOGRAPHY

1. ALBUQUERQUE SOARES, H. DE: *Sindrome urticariforme na malaria*, *Brasil-med.*, 1942, lvi, 431.
2. CHATTERJEE, S. C.: *Urticaria in malarial infection*, *Calcutta Med. Jr.*, 1939, xxxv, 291-293.
3. GOURIOU, E.: *Eruption morbilliforme et urticaire d'origine palustre*, *Bull. Soc. path. exot.*, 1938, xxxi, 614-617.
4. NIKOLAVO, N. D.: *Le paludisme chez les enfants au point de vue de l'allergie*, *Pediatrics*, 1939, 41-46.
5. SABLIN, P. E.: *Le paludisme sous le jour de la conception d'allergie*, *Vrach. delo.*, 1937, xix, 519-522.
6. SEN GUPTA, P. C.: *Urticaria due to malarial infection*, *Indian Med. Gaz.*, 1942, lxxvii, 416.
7. SHIRAKOGOROV, I. L.: *Pathomorphology of malaria from the view point of allergic reactions*, *Vrach. delo.*, 1936, xix, 345-354.
8. THONNARD-NEUMANN, E.: *Malaria und asthma*, *Arch. f. Schiffs-u. Tropen-Hyg.*, 1928, xxxii, 358-362.

ACQUIRED ARTERIOVENOUS FISTULA WITH COEXISTENT SUBACUTE BACTERIAL ENDOCARDITIS AND ENDARTERITIS *

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ACQUIRED arteriovenous aneurysms may result in fatal cardiac insufficiency because of the unfavorable circulatory dynamics set up by the shunt. Another and less common outcome results from the establishment of a subacute bacterial infection of the fistula. This complication has been reported by Bretschneider,¹ Walz,² Gravier,³ Porter and Williams,⁴ Hamman and Rienhoff,⁵ Leaman,⁶ and Touroff et al.⁷ In the first four cases named, there was also a coexisting bacterial endocarditis of the aortic valve. Our case, which has certain unique features, closely resembles the four cases cited and becomes the fifth such to be reported.

CASE REPORT

V. M., a 57 year old Italian longshoreman, was admitted to The Long Island College Hospital June 20, 1944, complaining of generally increasing dependent edema of two weeks' duration. Thirty years before, the patient had been struck by a pistol bullet in the upper anterior aspect of the right thigh. Within a week of the accident, he had noted the presence of a "buzzing," pulsating mass at the site of injury, which had persisted to the present time. Since then he had felt a heavy, dragging sensation in his right leg, and in recent years had noted slight dependent edema and a large chronic ulcerated area on the right shin. Aside from this, he had felt well enough to perform heavy work as a longshoreman until about three weeks prior to his admission. In 1941, the patient had been rejected for life insurance because of a "leaking valve." Since then he had suffered from occasional bouts of palpitation and mild exertional dyspnea. There had been no angina, orthopnea, or paroxysmal dyspnea. For some years he had a chronic non-productive cough, accompanied by substernal discomfort upon coughing.

Three weeks prior to admission the patient suddenly experienced severe pleuritic pain over the right anterior portion of the chest, made worse by the ever-present hacking, non-productive cough, and unaccompanied by hemoptysis. During this time there appeared gradually increasing bilateral dependent edema. At the same time palpitation and exertional dyspnea increased in severity so that the patient was forced to give up work. There were no bouts of angina or paroxysmal nocturnal dyspnea. He experienced drenching sweats at night and believed that his temperature was elevated, though no shaking chills were described. He lost 20 pounds in the two months preceding hospitalization. Past history: He had never had rheumatic fever, chorea, growing pains, joint pains, or scarlet fever. There were no frequent sore throats. He had a left mastoidectomy in 1924 and pneumonia in 1932. There was no history of penile sore, discharge, rash, or exposure to possible sources of venereal infection. The patient was a moderate wine drinker and in addition consumed three bottles of beer daily for many years.

The patient was a well-built, emaciated, pale, middle-aged, white Italian who was cooperative and well-oriented, but obviously ill. He was in the semi-upright position,

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with rapid and slightly labored respirations. There was no cyanosis of lips or ear lobes, but the skin and sclerae were slightly icteric. There were no spider angiomas. No petechiae were found in the conjunctivae. The fundi were normal. The gums were infected and the teeth were in poor repair. The tongue was rough, the mucous membranes pale. No petechiae were seen. There were violent, bounding carotid pulsations in the neck, but venous pulsations were readily differentiated. There was no nuchal rigidity. The trachea was in the midline and no tug was made out. There was no cervical adenopathy. The thyroid gland was normal in size and consistency. The thorax was very hairy, symmetrical and the expansion normal. Lung fields were resonant throughout, and tactile and vocal fremitus unimpaired, although there were moist râles at both bases. The apical impulse was forceful and diffuse and maximal in the sixth interspace, 14 cm. to the left of the midsternal line. The right border by percussion was 5 cm. from the midsternal line. There was a systolic thrill at the apex which corresponded to a grade V systolic murmur heard over the entire precordium and transmitted to the neck. There was a grade II systolic murmur at the aortic area followed by a dull second sound and a faint blowing diastolic murmur, transmitted to Erb's point. There was a sinus rhythm with rate of 90. Blood pressure was 160 mm. Hg systolic and 58 mm. diastolic in both arms, and both radial pulses were of the sharp, collapsing type. There was a capillary pulse in the fingers. A to-and-fro murmur was heard in the left femoral artery as well as a pistol shot sound. A good dorsalis pedis pulsation was present only in the left foot. There was a large, elongated, pulsating mass, 9 by 5 cm., in the antero-medial aspect of the right thigh beginning 4 cm. below Poupart's ligament. There was no discoloration or venous distention, and there was no difference in temperature between the two thighs. A systolic thrill and bruit were noted over the mass. By pressing the bell of the stethoscope well up under the right inguinal ligament a diastolic murmur and a pistol shot sound, much louder than the corresponding murmurs on the opposite side, were elicited. Immediately above the inguinal ligament, the right iliac artery was twice the diameter of the left, and its pulsations were correspondingly increased. The dorsalis pedis pulsation on the right was markedly diminished. The abdomen was not distended, but there were some dilated cutaneous veins up to the costal margin. There was no fluid wave or shifting dullness. The liver was palpable five fingers' breadth below the right costal margin. It was hard, smooth, rubbery, and non-tender. A moderately enlarged, firm, easily-displaced spleen was felt in the left upper quadrant of the abdomen. Other organs were not felt, and there was no tenderness or spasm. The genitalia were normal, with no penile scars. There was slight clubbing of the fingers and toes. No splinter hemorrhages, Janeway patches, or Osler's nodes were noted. There was moderate dependent pitting edema bilaterally up to the level of the knees. The right lower extremity was larger than the left. There was a large, depressed, pigmented, atrophic scar, 10 by 5 cm. over the right shin. Over both legs and on the back there were innumerable hemorrhagic spots (1 mm. in diameter) which showed various degrees of fading. The tendon and pupillary reflexes were normal.

On entry there was an erythrocyte count of 2.9 million with a hemoglobin of 10 grams (Haden-Hauser); a leukocyte count of 12,300, with 81 per cent polymorphonuclears, 17 per cent lymphocytes, 1 per cent monocytes, and 1 per cent eosinophiles and a sedimentation rate (Westergren) of 120 mm. per hour. The urine had a faint trace of albumin, a specific gravity of 1.023, and there were positive tests for bile and urobilinogen in the urine. Sediment was negative. The Wassermann reaction was 2+, Kline diagnostic 1+, the Hinton test positive, and the Frei test negative. Blood sugar was 78 mg. per 100 c.c., urea nitrogen 14.8 mg., uric acid 3.5 mg., total protein 8.2 gm., with an albumin of 2.6 gm. and a globulin of 5.4 gm. The icterus index was 14 with an immediate direct van den Bergh of 1.3 mg. per cent; chlorides were 563 mg. The cephalin flocculation test was 4+.

The prothrombin time was 90 per cent of a normal control, and vitamin C 0.4 mg. per 100 c.c. Bleeding time was 2 minutes; clotting time, 3 minutes. The Good-pasture test for solution of blood clot was normal. Electrocardiogram on admission showed a sinus rhythm of 96, PR interval of .16. ST_2 was elevated and ST_1 depressed 1 mm. each; ST_4 depressed 5 mm. with initial deflection downward. There was a left axis deviation. This was interpreted as myocardial disease of the left ventricular strain pattern. On admission, roentgen-ray studies revealed marked calcification and tortuosity of the vessels of the right thigh, hepatomegaly and splenomegaly. There was an elongated aorta, pulmonary congestion, and marked cardiac enlargement both to the right and left.

Course: The patient was placed on a low salt diet with moderate fluid restriction and was started on slow digitalization. Satisfactory diuresis ensued and, in spite of a low grade fever, the patient appeared somewhat better the day after admission. On the fifth hospital day, June 25, the patient experienced a sharp pleuritic-type pain in the right axilla and began to raise a frankly bloody sputum. His temperature spiked to 105° F., pulse rose to 125, and respirations increased to 45 per minute. Bronchovesicular breath sounds and parenchymatous râles were heard in the right axilla. No dullness was demonstrated. A pneumonic infiltration of the right lower lung field was noted by roentgen-ray. Sputum culture yielded *Staphylococcus aureus*, an untypable pneumococcus, *Neisseria flava*, and *Hemophilus influenzae*, all in moderate numbers. Three blood cultures taken June 29, June 30 and July 1 yielded no organisms aerobically or anaerobically; those taken on July 12, July 14 and July 15, each yielded *Streptococcus viridans*, 2 to 4 colonies per c.c., in 10 to 14 days after being taken, six days after the patient's death. Full doses of sulfamethazine were given, and the temperature dropped to an intermittent type of fever ranging between normal and 101.8°. Sulfamethazine levels averaged about 7.0 mg. per 100 c.c. White blood cells numbered 15,000, with 80 per cent polymorphonuclears. Urine showed no additional abnormalities. At this time auricular fibrillation ensued at a rate of 120. The dosage of digitalis was increased, bringing the ventricular rate down to 80. Because of the failure of the sulfonamide to control the fever, penicillin was substituted for sulfamethazine in doses of 15,000 units intramuscularly every three hours. This was continued for five days and discontinued as the patient was afebrile but still showed no subjective or objective signs of improvement.

At this time further investigation of the arteriovenous fistula was undertaken. Obliteration of the shunt by manual pressure caused an immediate rise in systolic blood pressure of 40 mm. of mercury (Branham phenomenon), without significant decrease of the pulse rate. This failure to slow the pulse was probably due to the inactive carotid sinus reflex. A control procedure on the left side changed neither the systolic blood pressure nor the pulse rate. From this time until death the patient had a remittent type of fever from 99° to 101° F. There appeared numerous crops of tiny hemorrhagic spots similar to those previously described. Urine sediment remained free from red blood cells until the last few days of life, at which time a rare red blood cell per low power field was found. No splinter hemorrhages or petechiae were found on the mucous membranes. The icterus index increased to 24; total protein was 8.2, gm., with an albumin of 1.6 gm. and a globulin of 6.6 gm. The arm to lung circulation time was 23 seconds (ether); venous pressure was 150 mm. of saline on July 17. A prothrombin time on this date was normal. During the last week of life, the patient complained of generalized abdominal pain. The abdomen was distended and tympanitic; free fluid was demonstrated. On the last day of life, abdominal pain and distention increased greatly, the temperature spiked to 103° F., and the respirations increased to 60. Wangensteen suction, repeated Harris drips, neostigmine and morphine were useful in decreasing the distention. However, the patient lapsed into coma, and in spite of supportive therapy, died on the twenty-eighth hospital day.

Pathological Report. An autopsy was performed by Dr. Jean Oliver nine hours after death.

Gross: The peritoneum over all the abdominal viscera was intensely congested and bright red, an appearance which apparently was due to a great number of small confluent petechial hemorrhages. The liver projected about 2 fingers'-breadth below the costal margin. The external surface was roughly granular.

The heart was about two and a half times the size of the fist, weighing 720 grams. The left side was enlarged and quite firm. The right ventricle was even more greatly enlarged and was filled with postmortem clot and fluid blood. The tricuspid orifice admitted three fingers and the mitral orifice the tips of three fingers. The mitral valves were quite smooth and showed an occasional yellow atheromatous spot. Attached to all three of the aortic valves at about the center of each flap were soft, irregular vegetations measuring roughly 2 mm. to 5 mm. in diameter. These vegetations covered ulcerations in the valve flap. The remaining valve flap tissue was definitely thickened and in the posterior cusp at its base was a mass of calcareous material about 2 mm. in diameter. The orifice of the left coronary artery was widely patent. Its course was tortuous, and there were some atheromatous plaques in its wall. The right coronary was also very tortuous and its walls were thickened, but there was no apparent interference with the lumen of either vessel. The aorta lay in its usual position and was of normal calibre.

The intima of the aorta was quite smooth above the valve. In the upper thoracic portion were a moderate number of atheromatous spots and plaques. These increased in frequency in the abdominal portion of the vessel and there showed calcification and some ulceration. There were no recent evidences of splenic infarction. The liver weighed 1660 grams and measured 24 by 16 by 9 cm. The left lobe was deformed by superficial scars which extended a slight distance below the surface of the organ. On the cut surface there was marked jaundice of the hepatic tissue and an irregular mottled pattern due to extreme irregular congestion of the parenchyma.

The left common iliac artery arose in a normal manner and passed down into the pelvis in its usual way. At its origin it was 2.75 cm. in circumference. Its wall was thick. The right common iliac artery was considerably dilated at its origin, the circumference measuring 5.5 cm. Its wall was also thickened and showed scattered atheromatous plaques and some small ulcers. Two cm. below the exit of the ileolumbar artery the right external iliac suddenly dilated into an irregular saccular cavity whose greatest dimension was about 8 cm. An irregular series of dilatations extended for about 13 cm. down the course of the artery, so that the tortuous vessel lay along the brim of the pelvis and was covered and bound down by a mesentery-like fold of peritoneum. The wall of these aneurysmal sacs was less than 1 mm. in thickness and contained thin calcified plates. Below the saccular dilatations just described the femoral artery passed into Hunter's canal and again assumed its former diameter of about 5 cm. Here the wall was quite thick. At a point 13 cm. below the last aneurysmal sac mentioned above and 4 cm. below the exit of the profunda femoris was another single aneurysm which measured 7 cm. in diameter and 8 cm. in length. Its wall was quite thin and in part calcified. Below this second aneurysmal sac the femoral artery was reduced in diameter to about 2 cm. and was heavily calcified. Just below the lowermost aneurysm was an orifice in the wall of the artery, 1 cm. in diameter, which led to a communication that passed upward and back to the femoral vein. At the point of junction of vein and artery there was a calcareous mass 1 cm. in diameter covered and infiltrated with thrombotic material. From this point on, the femoral artery proceeded downward in its usual course. The profunda femoris arose in its normal position. It passed through a mass of dense connective tissue scar in a tortuous course. Its wall was thickened and calcified. No single venous trunk was found below the communication between artery and vein. Several large

veins joined, however, to form a femoral vein which lay in its usual relation to the artery. The vein was greatly and irregularly dilated, some stretches measuring only 2 cm. in diameter and others forming pouch-like varices 20 cm. in diameter. At its junction with the common iliac the vein was 7 cm. in diameter. In spite of the stretching the wall was thick and normal valves were seen in it.

Microscopic: Ventricle: The muscle fibers throughout the section showed a moderate increase in size. The nuclei were well stained, and there was no evidence of necrosis. The small arteries showed in general a definite thickening of their walls, but the connective tissue about them in most cases was free of inflammatory cells. Occasionally, however, in the periarterial regions were collections of mononuclear cells and large irregular cells with large, clear, oval nuclei and a prominent nucleolus. In some instances these cells were arranged in nodule-like clusters that included part of the wall of the small artery.

Aortic Valve: Sections showed a marked hyaline thickening of the valve tissues. There was extensive destruction of this fibrous tissue, and on its surface was a large thrombus in which masses of bluish-staining bacteria might be seen. Apart from the septic thrombus, there were other small fibrinoid nodules which showed no bacteria. Beneath these the valve tissue was filled with large irregularly shaped cells, many with more than one nucleus. The nuclei were large and vesicular and had prominent nucleoli. None of these cells was found about the base of the mitral valve or in the region of the annulus fibrosus. Gram stain showed occasional small chains of diplococci in the septic thrombus. The aorta showed a hyaline thickening of the intima to a moderate degree. The muscle of the media was well preserved.

There was a marked fibrous thickening of the capsule of the liver, and from this thickened capsule bands of connective tissue ran down into the parenchyma of the organ for a considerable distance. There was a moderate increase in the connective tissue in the peri-portal regions and in some places a considerable round cell infiltration. The capillaries between the hepatic cords in many areas showed a marked dilatation with atrophy of the hepatic cells. This passive congestion was more pronounced near the surface of the organ.

Small Intestine: There was a marked edema of the submucosa, muscularis and serosa. In the edematous tissue were scattered leukocytes, both mononuclear and polymorphonuclear. Beneath the serosa there were many red blood cells, and a relatively lesser number of leukocytes. Gram stain did not show any bacteria.

COMMENT

Many of the changes in cardiovascular dynamics due to arteriovenous fistulae have been understood since the time of William Hunter (1757), but the studies of Emile Holman and his coworkers have clearly defined and elucidated these changes.^{8,9} There is now general agreement that in the presence of a moderate or large arteriovenous fistula of appreciable duration, the following changes occur: (1) Increase of circulating blood-volume. (2) Increase in cardiac output. (3) Increase in pulse pressure. (4) Hypertrophy and dilatation of the heart. (5) Increased local venous pressure both proximal and distal to the fistula. Presumably, a generalized rise of venous pressure does not occur until cardiac insufficiency supervenes.

In addition to the general circulatory changes that result from an A-V fistula, certain localized alterations of the aortic valves are of prime importance because these changes supply the nidus for the later development of a bacterial endocarditis. In this case, because of the absence of the commoner endocardial altera-

tions due to rheumatic, syphilitic or congenital heart disease, minor benign changes of the heart valves are thrown into prominence.

Gouley and Sickel¹⁰ have recently described a characteristic lesion of the aortic valve occurring in cases of aortic regurgitation resulting from stretching of the aortic ring. "This lesion is a sclerotic thickening confined to the mid-portion of the free edge of the aortic leaflets. It is essentially a loss and fibrous replacement of the original corpora arantii, without involvement of the lateral portions of the free margin of the leaflet or of the body of the leaflet, except insofar as marked central involvement necessarily extends some distance toward the periphery." Together with this marginal fibrosis, Gouley and Sickel describe elongation of the aortic leaflets with deepening of the sinuses of Valsalva and dilatation of the aortic ring (greater than 7.5 cm.). The aortic valve commissures of some of their cases were stretched apart without loss of the sharpness of the adjoining

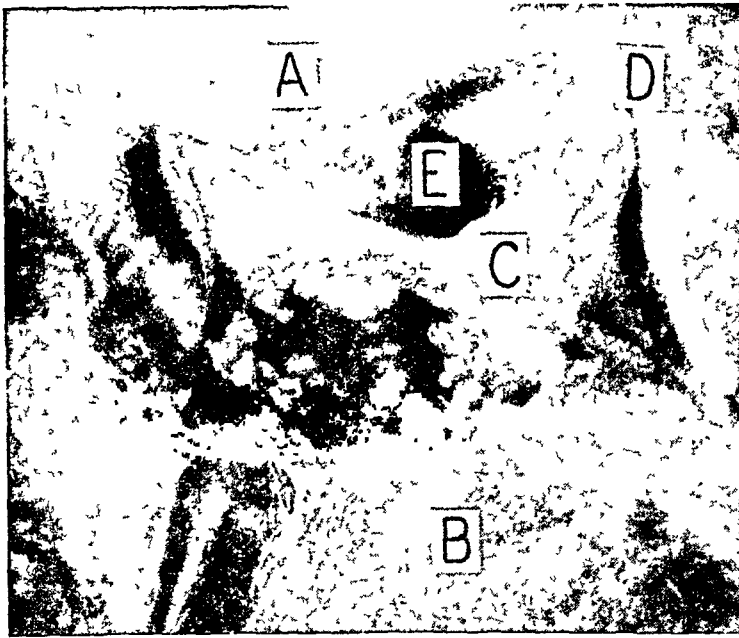


FIG 1 Aortic valve A—left atrium, B—left ventricle; C—left posterior valve cusp with its ulcerating vegetation, D—commissure. Note the sharpness and the lack of widening and overgrowth E—deepened sinus of Valsalva

free margins of the valves. This change is said to be quite distinct from the overgrowth and extension of syphilitic aortitis into the commissures. It will be noted that the marginal sclerosis resembles the rolled cord-like edge of the syphilitic aortic valve, which is not surprising if the underlying cause of the valve changes in both types of regurgitation is the dilatation of the aortic ring. Even those cases of hypertensive heart disease which exhibit this valve change without dilatation of the aortic ring, as measured at necropsy, may fall into this classification in view of the tremendous "dynamic dilatation" of the aorta present during life. The aortic valves in our case (figure 1) presented the changes described above. The lengthening of the valve leaflets, the depth of the sinuses of Valsalva and the sharp edges of the commissures are clearly demonstrated. The aortic ring measured 9.5 cm. in circumference, and the base of the arch was entirely free

from the changes typical of syphilitic aortitis. We believe that this aortic valve was not the seat of syphilitic infection in spite of the positive serological tests for syphilis because of the absence of the diagnostic gross and microscopic features of this condition—destruction of the medial elastic fibers of the aorta, dilatation, fine wrinkling and coarse scarring of the intima, thickening of the adventitia, widening of the commissures, perivascular inflammation and necrotic mesaortitis. We believe that the aortic valve was not the seat of rheumatic infection because of the lack of valvular scarring and distortion. We feel that the collections of atypical mononucleated cells scattered throughout the myocardium are not true Aschoff bodies but are the "wandering mononuclear cells" seen in subacute bacterial endocarditis. Credence is lent this view by the relative scarcity of these cells at the base of the mitral valve, the location where these cells are most numerous in rheumatic carditis.^{11, 12}

Our reconstruction of the pathogenesis, therefore, is as follows: The bullet wound established at least a moderate sized fistula as judged by the presence of a "buzzing, pulsating mass" easily perceived by the patient. During the next three decades, marked hypertrophy and dilatation of the heart appeared. The resultant stretching of the aortic ring was for a time compensated by the lengthening of the aortic valve leaflets, but eventually, aortic insufficiency ensued. As a result of the high pulse pressure, with forceful snapping of the supple leaflets at the onset of each diastole, hypertrophy of the corpora arantii and the changes described by Gouley and Sickel occurred. Cardiac insufficiency set in, and finally, *Streptococcus viridans* became implanted upon the aortic valves and the margin of the fistula, and subacute bacterial endocarditis and endarteritis were established. The oral sepsis may have provided the source for the blood stream infection.

Our case presents a number of points of considerable clinical interest. Among these are the jaundice, the positive serological tests for syphilis, the pattern of atherosclerosis, and a capillaritis of the skin and serosa. The patient was icteric throughout his hospital course. The liver was palpable five fingers' breadth below the costal margin and the spleen was easily felt in the left upper quadrant. Liver function tests indicated impaired function. Cephalin flocculation was 4; albumin was depressed to 1.6 gm. with a globulin of 6.6 gm. (Frei test was negative). These facts together with a history of consumption of wine and beer for many years led us to believe that a cirrhosis of the liver was present, which was made more severe by the long-standing anoxemia due to chronic passive congestion.^{13, 14} On necropsy there was noted scarring of the liver with moderate increase of periportal connective tissue. The patient therefore had early cirrhosis of the liver, which, aggravated by the passive congestion, further increased the difficulty of diagnosis.

The positive Wassermann and Hinton tests were also of more than passing interest. In retrospect, we feel that since there was no pathological evidence of syphilis, the serological tests for syphilis were false positives due either to the jaundice, to the endocarditis, or to hyperglobulinemia, although latent syphilis cannot be absolutely ruled out. The fact that the titers were low lends further support to this belief. Hyperglobulinemia may cause false positive serological tests for syphilis, and, in this case, is the probable cause for these reactions. The hyperglobulinemia may have been due to the cirrhosis as well as the subacute bacterial endocarditis.

It will be seen in figure 2 and in the gross pathological description that the right common iliac, external iliac, and femoral arteries are considerably dilated and tortuous as compared with the normal left-sided vessels. In addition to this obvious expression of increased blood flow, there is also a tremendous increase in the amount of atheromatous change and ulceration of the intima on the affected side. It has been stated¹⁵ that there is an increased tendency to the deposition of



FIG 2. A—abdominal aorta; B—right common iliac artery, and below, right external iliac artery; C—left common iliac artery; D—femoral arterial aneurysms; E—femoral artery.

cholesterol in the walls of vessels subjected to marked turbulences, eddy currents, rapid changes of pressure, or other changes which may set the walls vibrating. If this is true, the extensive change of the affected vessels need not surprise us.

The purpuric eruption noted during life over the legs and back was of considerable interest in view of the normal prothrombin, plasma and vitamin C levels, and the normal Goodpasture test. The parietal peritoneum and the serosa

of the small intestines were found at autopsy to be "bright red" owing to innumerable, densely scattered petechial hemorrhages. This finding is thought to be an unusual response of the capillaries to the streptococcal proteins.

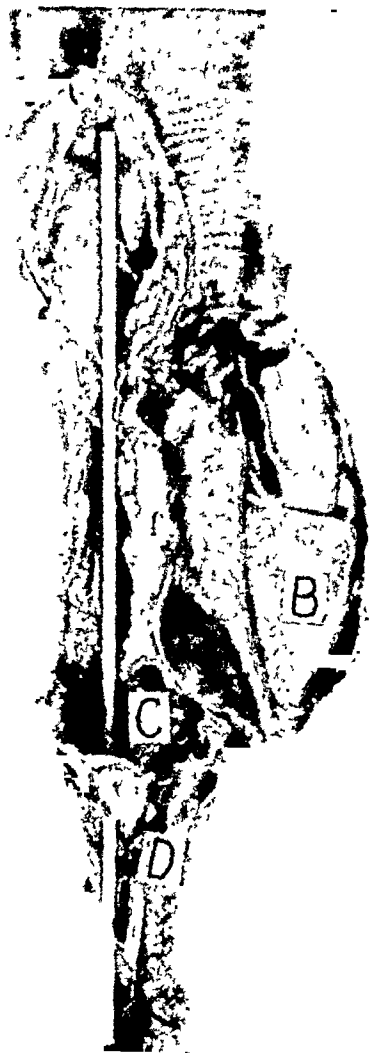


FIG. 3. A—femoral artery (proximal); B—arterial aneurysmal sac; C—infected thrombotic material; D—femoral artery (distal); the probe lies in the femoral vein, and passes through the arteriovenous fistula between C and D. *Note:* The arteriovenous aneurysm shown in figure 3 is distal to, and connected with the multiple arterial aneurysms seen in figure 2 by normal femoral artery, E in figure 2.

CONCLUSIONS

1. This is the fifth reported case of acquired arteriovenous aneurysm of the femoral artery and vein, complicated by subacute bacterial endocarditis of the aortic valve and by bacterial endarteritis of the fistula.

2. The aortic valve was the seat of a "mechanical sclerosis" similar to that in hypertension, thus supplying the nidus for the endocarditis.

3. Other findings of clinical interest are noted and discussed.

BIBLIOGRAPHY

1. BRETSCHNEIDER, H.: Mykotische Auflagerungen in einem Aneurysma arterio-venosum indirectum bei Endocarditis lenta, Frankfurt. Ztschr. f. Path., 1923, xxix, 528-542.
2. WALZ, K.: Aneurysma arterio-venosum mit mykotischen Auflagerungen bei Endocarditis lenta, Deutsch. Ztschr. f. d. ges. gericht. Med., 1925, vi, 366-369.
3. GRAVIER, M. L.: Un cas de coexistence d'insuffisance aortique et d'aneurysme arterio-veineux, endocardite infectieuse secondaire, Lyon méd., 1929, cxliii, 549-552.
4. PORTER, W. B., and WILLIAMS, G. Z.: Subacute *Streptococcus viridans* infection on an arterio-venous aneurysm and the aortic valves: A case report, Trans. Assoc. Am. Phys., 1939, liv, 359-365.
5. HAMMAN, L., and RIENHOFF, W. F.: Subacute *Streptococcus viridans* septicemia cured by excision of an arteriovenous aneurysm of the external iliac artery and vein, Bull. Johns Hopkins Hosp., 1935, lvii, 219-239.
6. LEAMAN, W. G., JR.: The prognosis in heart disease with special reference to curable types, New Internat. Clin., 1939, iii, 137-140.
7. TOUROFF, A. S. W., LANDE, H., and KROOP, I.: Subacute *Streptococcus viridans* septicemia, cured by excision of an infected traumatic arteriovenous aneurysm. Surg., Gynec., and Obst., 1942, lxxiv, 974-982.
8. HOLMAN, E.: Arteriovenous aneurysms, 1937, Macmillan, N. Y.
9. HOLMAN, E.: Anatomical and physiologic effects of arterio-venous fistulae, Surgery, 1940, viii, 362-382.
10. GOULEY, B. A., and SICKEL, E. M.: Aortic regurgitation caused by dilatation of the aortic orifice and associated with a characteristic valvular lesion, Am. Heart Jr., 1943, xxvi, 24-38.
11. GROSS, L., ANTOPOL, W., and SACKS, B.: Standardized procedure suggested for microscopic studies on the heart, Arch. Path., 1930, x, 840-852.
12. GROSS, L., and EHRLICH, J. C.: Studies on the myocardial Aschoff body, Am. Jr. Path., 1934, x, 467-504.
13. CAMPBELL, J. A.: The problem of Mount Everest, Lancet, 1928, ii, 84-86.
14. RICH, A. A.: Pathogenesis of the forms of jaundice, Bull. Johns Hopkins Hosp., 1930, xlvii, 338-377.
15. HUEPER, W. C.: Arteriosclerosis, Arch. Path., 1945, xxxix, 51-65.

PAROXYSMAL VENTRICULAR TACHYCARDIA: REPORT OF A CASE SHOWING THE PHASES OF RECOVERY RECORDED BY ELECTROCARDIOGRAPH*

By JAMES A. COLLINS, JR., M.D., *Danville, Pennsylvania*

THE uncommon finding of paroxysmal ventricular tachycardia with the phases of recovery recorded by electrocardiograph prompted this communication. The usual prognosis in such a case is quite grave, and since this patient recovered under therapy in spite of serious myocardial damage, it was thought worth while to report it.

CASE REPORT

W. E., a white male, aged 64, was admitted to the hospital by ambulance. He had suffered from a severe attack of precordial pain two years previously. The pain

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radiated down the left arm and was accompanied by dyspnea, weakness, and perspiration. Apparently, this was a coronary occlusion, although it was never proved. Following his recovery, there was persistent angina pectoris on slight exertion, dyspnea, and weakness. The present illness began two days prior to admission. It was characterized by excruciating, vice-like chest pain, marked dyspnea, and weakness. A hypodermic given by his local physician relieved the pain, only to have it return again in a few hours. The patient was then referred to the hospital for further treatment, the provisional diagnosis being acute coronary occlusion.

The physical examination revealed an elderly male, critically ill. He was markedly dyspneic, orthopneic, and cyanotic. The temperature was 98°, respirations 28 and blood pressure 82 mm. Hg systolic and 40 mm. diastolic. The cardiac rate was 200 to 250 at the apex and only 60 at the wrist. The mouth showed poor dental hygiene, and there was chronic infection of the pharynx. The veins of the neck and

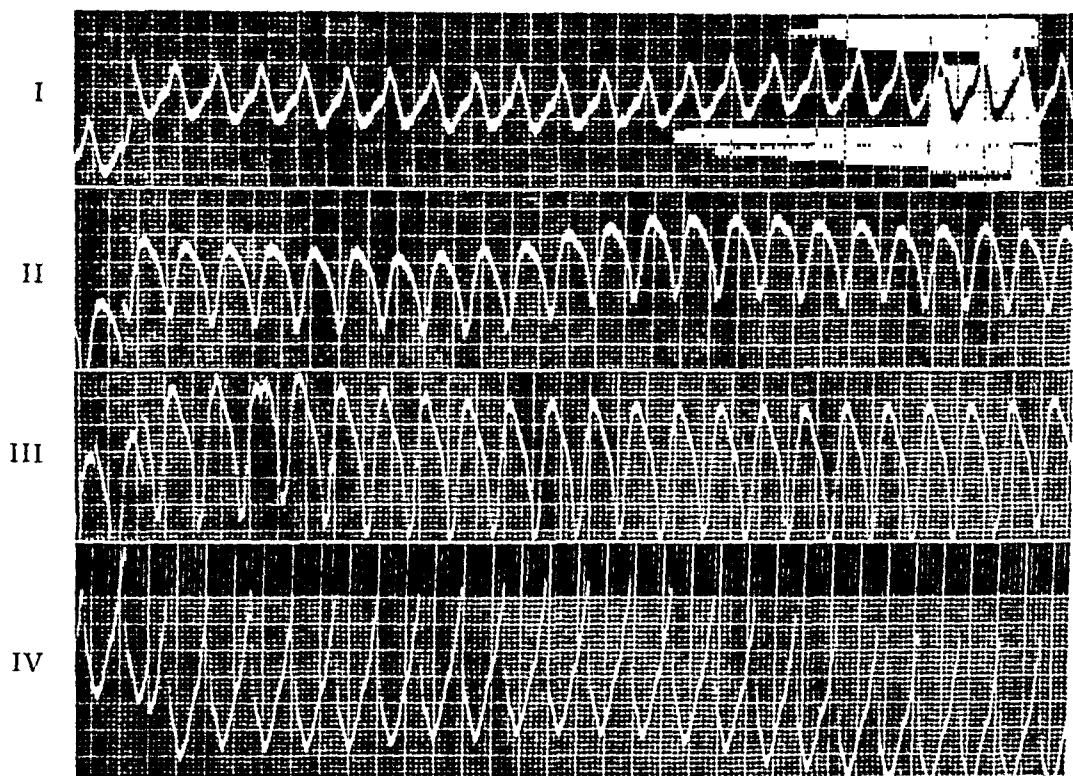


FIG. 1. Ventricular tachycardia, rate 196, taken on admission.

chest were distended, and pulsations were quite prominent. The lungs were relatively clear. The heart was not enlarged, and the rhythm was considered regular. There were no audible murmurs. The liver was palpably enlarged and tender, and the abdomen was distended with gas. Peripheral vessels revealed a moderate degree of sclerosis. There was no peripheral edema.

The urinalysis and blood count were both entirely normal, with 6350 leukocytes. The blood Wassermann reaction was negative. A portable electrocardiograph taken shortly after admission showed ventricular tachycardia (figure 1). Treatment consisted of strict bed rest, intranasal oxygen, at first morphine, and later papaverine. Digitan was administered intramuscularly for one dose, then digitalis was given daily, grains 1½, for three additional days. Quinidine sulfate was started the day after admission, with a dose of 5 grains every two hours. This was increased to 15 grains

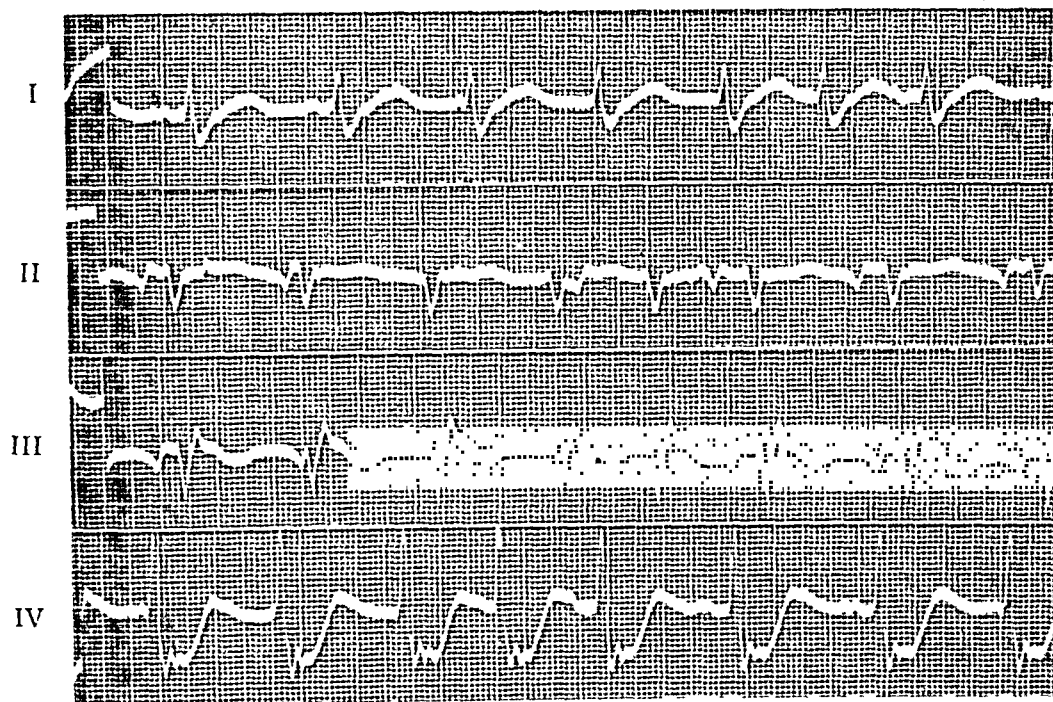


FIG. 2. Complete heart block with irregular ventricular beat, rate 67. Probable recent coronary occlusion, sixth hospital day, after quinidine therapy.

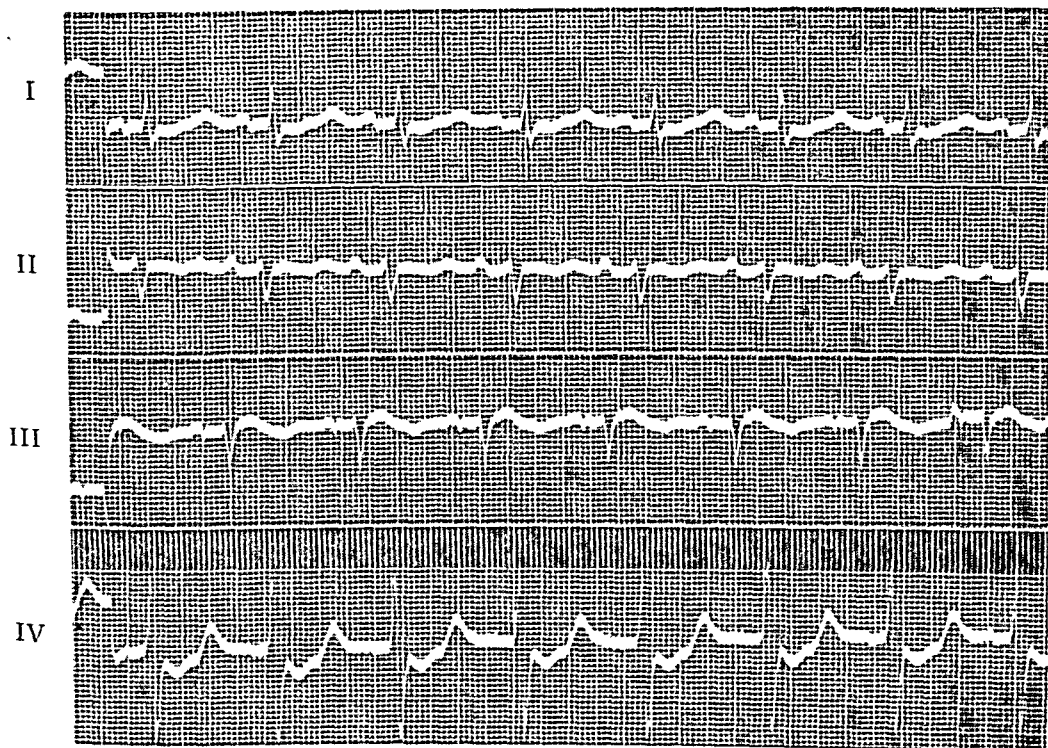


FIG. 3. Sinus rhythm, first degree heart block. Rate 65, seventh hospital day.

every two hours for five doses daily until a total of 210 grains had been administered within 80 hours. Digitalis was discontinued at this point. Throughout all this medication, there was no appreciable change in cardiac rate or status. The day after discontinuing digitalis, while continuing quinidine, the pulse rate became quite slow, recorded as 60. An electrocardiographic tracing revealed complete heart block with an irregular ventricular beat, and also T and RT changes compatible with a recent coronary occlusion (figure 2). This was the sixth hospital day. On the seventh hospital day the cardiac rate was regular, no pulse deficit was present, and the electrocardiograph indicated sinus rhythm, first degree heart block, and coronary occlusion (figure 3). Digitalis was given in place of quinidine, because neither quinidine sulfate nor hydrochloride was available at the time the patient was admitted.

The patient progressed through a normal convalescence for the next week in the hospital without any further cardiac difficulty. He was discharged then to continue his convalescence at home.

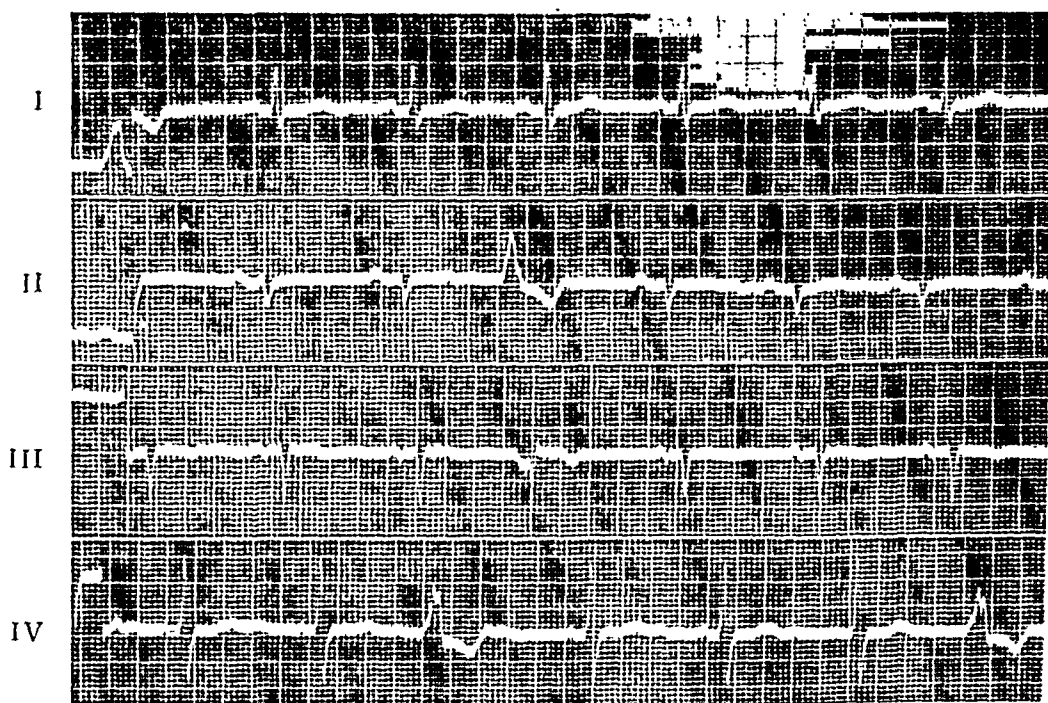


FIG. 4. Ventricular premature contractions. Rate 60, six months later.

The patient returned for a follow-up visit six months later. At this time, he had no serious complaints referable to the cardiovascular system. The examination of the heart showed an irregular rhythm, sounds of fair quality with no murmurs heard. An electrocardiogram at this time revealed ventricular premature contractions with considerable myocardial damage. The T-waves were compatible with an old myocardial infarction (figure 4).

SUMMARY

A case of rapid ventricular tachycardia associated with recent coronary occlusion is reported. The rhythm progressed through ventricular tachycardia, complete heart block, first degree heart block, and normal sinus rhythm under treatment. The treatment consisted of heavy doses of quinidine sulfate, 15 grains

every two hours for 10 doses; and later five grains three times a day after cessation of the ventricular tachycardia. It is believed that digitalis is contraindicated and tended to maintain the tachycardia. It was after discontinuing digitalis that the effect of the quinidine was manifest. The tachycardia continued throughout eight days with no abatement, but ceased shortly after all digitalis was discontinued, while quinidine therapy was continued.

CONCLUSIONS

1. Quinidine sulfate is the drug of choice in the treatment of ventricular tachycardia.
2. Digitalis is harmful and acts against the effect of the quinidine sulfate in the treatment of this condition.
3. Rather large doses of quinidine sulfate are tolerated, apparently without much difficulty.

EDITORIAL

BAL IN THE TREATMENT OF ARSENIC AND MERCURY POISONING

THE term BAL is a contraction for British Anti-Lewisite, a compound developed by Peters, Stocken, and Thompson¹ during the recent war as an antidote to the arsenical blister gases. The chemical name for BAL is 2,3-dimercaptopropanol. First intended for the local decontamination and treatment of the skin and eyes, this compound was subsequently found to be effective in the systemic treatment of severe arsenic poisoning, not only after exposure to the arsenical blister gases but also when this occurs as a complication of arsenotherapy. More recent experimental and clinical observations have demonstrated that BAL exerts an equally striking protective and therapeutic effect in mercury poisoning.

In order to make available the research work which is the basis for the therapeutic use of BAL, a committee, consisting of representatives of the various groups which had participated in the BAL study, was appointed to plan and carry out publication of the experimental data. Under the chairmanship of Dr. Warfield T. Longcope, the committee decided that papers on the fundamental work on BAL be selected and divided into three groups: those dealing with biochemistry, those dealing with toxicology, and those dealing with clinical applications. The *British Biochemical Journal*,² the *Journal of Pharmacology and Experimental Therapeutics*,³ and the *Journal of Clinical Investigation*⁴ were considered to be especially suitable for publishing the papers selected in the form of a symposium.

There is now a convincing body of evidence that the toxic effects of arsenicals are referable primarily to the fact that they combine with $-SH$ groups in the tissues and thus block one or more physiologic systems critical to the cellular economy. It was further shown that these toxic effects were not only prevented but could actually be reversed by $-SH$ compounds. The implication that the toxic action of arsenicals is referable to the inactivation of $-SH$ -containing enzyme proteins in living cells is clear.

Simple dithiol compounds form relatively stable ring compounds with Lewisite and other trivalent arsenicals. Of the various dithiols tried out BAL, or 2,3-dimercaptopropanol, recommended itself particularly as a local decontaminant in combating the arsenical blister gases when applied to the skin or eyes in ointment form. The action of BAL is ascribed to the fact that, by reacting with arsenicals to form a stable ring compound, it can effectively compete for the arsenical with the thiol groups of tissue proteins.

¹ PETERS, R. A., STOCKEN, L. A., and THOMPSON, R. H. S.: British Anti-Lewisite (BAL), *Nature*, 1945, clvi, 601.

² *Biochem. Jr.*, 1946, xl, 513—6 articles.

³ *Jr. Pharm. and Exper. Therap. (Supplement)*, 1946, lxxxvii—125 pages—15 articles.

⁴ *Jr. Clin. Invest.*, 1946, xxx, 451—11 articles.

This competition involves two distinct processes: (1) combination with the toxic arsenical before it combines with tissues; (2) removal of arsenic from the tissues after it has already combined, with the formation of BAL-thioarsenite from the tissue protein-thioarsenite and the release of the tissue thiol groups.

BAL, administered topically, subcutaneously, intramuscularly, or intravenously to animals, exerted both protective and therapeutic effects against local and systemic injury by toxic arsenicals. Toxic side-effects from effective doses were not serious in the experimental animals; hence it seemed safe to proceed with cautious trials of BAL therapy in patients with arsenical poisoning.

Pharmacologic observations and toxicity studies on BAL in man revealed the following points of interest: Atopical application of BAL in the form of a 5 per cent ointment is safe, although it may cause local irritation. Skin sensitization to BAL developed in only 19 per cent of the individuals tested when the ointment was applied to normal skin, but in 66 per cent when the ointment was applied to damaged (burned) skin. Parenteral administration of up to 5 mg. per kilogram every four hours for four doses will produce no lasting damage in the average normal individual, although certain transitory toxic effects were noted in many instances. These toxic effects consisted of paresthesias, perspiration and a sense of warmth, pains in the limbs, jaws, abdomen, and head, lacrimation, blepharospasm, salivation, vomiting, unrest, apprehension, weakness, fatigue, tachycardia, and transitory hypertension. The minimal dose producing toxic effects lies between 3 and 5 mg. per kilogram. A 10 per cent solution of BAL in peanut oil and benzyl benzoate proved to be most satisfactory for intramuscular administration. In normal men and those exposed to minimal quantities of an arsenical smoke a single injection of BAL in dose of 3 to 5 mg. per kilogram was regularly followed by a significant increase in the rate of urinary arsenic excretion.

Reports from both England and this country attest to the beneficial effects of both topical and parenteral administration of BAL in the treatment of arsenical dermatitis. Victims of intractable localized dermatitis caused by diphenylamine chlorarsine improved rapidly with the application of BAL ointment, which was, however, quite painful when applied to the inflamed skin. Since intramuscular injections were much less disturbing, this route of administration soon became the preferred method of treatment. Patients with exfoliative dermatitis from antisyphilitic arsenicals improved with either local or parenteral therapy. The duration of the dermatitis was distinctly shortened, although mild recurrences were frequent if treatment was not continued for at least one week. With an average intramuscular dose of 300 mg. per day, no serious constitutional reactions were encountered. The English workers report no significant change in the excretion of arsenic that could be attributed to BAL in their dermatitis patients, whereas the American group found a consistent increase in arsenic excretion after BAL therapy of arsenical dermatitis, corresponding to the good clinical response of these

patients. No such regular improvement was evident, either clinically or in the excretion of arsenic, after BAL therapy in jaundiced patients with toxic hepatitis attributed to arsenical poisoning.

Eagle⁵ in summarizing clinical experience with BAL reports that this compound has been used in more than 200 cases of various types of arsenic poisoning with results that indicate that the danger of some complications may be markedly reduced by its early administration in adequate dosage. He concludes that BAL must be given early in somewhat larger doses than were originally recommended. In the severe complications, a dose of 3 mg. per kilogram should be injected every four hours for the first two days, followed by a similar injection every six hours on the third day and twice daily thereafter for two days, or until complete recovery. In 88 cases of arsenical dermatitis, 51 being typical exfoliative dermatitis, definite improvement was noted in 80 per cent of the exfoliative cases within three days with complete recovery within an average of 13 days. In 55 patients with hemorrhagic encephalitis caused by intensive arsenotherapy, 40 of whom were either convulsing or comatose when BAL was given, recovery followed in 44 within one to seven days. Ten of 11 patients with arsenical agranulocytosis recovered under BAL therapy; increase in the total white blood cell count and an even more pronounced increase in polymorphonuclears was usually apparent within two days, and the white count approached normal within one week. On the other hand, BAL in the dosage used had no effect in three cases of aplastic anemia occurring as a complication of arsenotherapy. Although the clinical response of jaundiced patients to BAL was less dramatic, the symptomatic improvement in five of 14 cases was so prompt that it appeared to be due to the use of BAL. Of four patients who were erroneously given a massive overdose of mapharsen, the three who received prompt and adequate treatment recovered rapidly.

Pertinent to the background of the study of the effects of BAL in mercury poisoning were the observations supporting the general hypothesis that other heavy metals besides arsenic are toxic to biological systems because of their reaction with SH groups of the protein moiety of cellular enzymes to form mercaptides. Mercury shares in this action and BAL has been shown to be capable of reactivating enzyme systems poisoned by mercury. In experimental animals BAL exerts a striking protective action from poisoning by bichloride of mercury given orally or intravenously. Remarkable protection was noted in dogs even if the administration of BAL was delayed for two to five hours after the oral administration of otherwise lethal doses of mercury.

On the basis of the encouraging results noted in experimental animals, a clinical study of the effects of BAL in mercury poisoning was instituted by Longcope and his associates. Twenty-three patients suffering from bichloride of mercury poisoning were treated by intramuscular injections of BAL with only one death, although 15 of these patients had ingested sufficient

⁵ EAGLE, H.: The systemic treatment of arsenic poisoning with BAL (2,3-dimercaptopropanol), Jr. Vener. Dis. Inform., 1946, xxvii, 114.

mercury to have been lethal in a high percentage, had no specific treatment been administered. A total of 450 to 750 mg. were injected during the first 12 hours with a total dosage of 900 to 2870 mg. over the first three or four days. Considerable importance was attached to the prompt treatment by BAL in an initial injection of 300 mg., followed within the first 12 hours by two or three further injections of 150 mg. each. Toxic effects of BAL were observed in a few patients. Perhaps the most significant effects of treatment were the prompt relief of even the most alarming symptoms, when BAL in sufficient doses was administered within three to four hours after the bichloride of mercury had been swallowed, and the rapidity with which the patients made a complete recovery. In the only fatal case in the series, treatment could not be started until 13 hours after the ingestion of the poison. In the same paper the authors mention briefly 19 additional cases of bichloride poisoning treated with BAL with only one death, or a total of 42 patients treated with only two deaths! These figures speak for themselves in acclaiming the truly miraculous protective action of BAL in clinical mercury poisoning.

So much for the remarkable antidotal action of BAL in the treatment of arsenical and mercurial poisoning. Experimental work suggests that this chemically simple dithiol may prove to be equally effective in the prevention or treatment of poisoning from other heavy metals. War is rightly regarded by civilized man as an unmitigated evil, but, if there is any consolation to be gained therefrom, it lies in the tremendous impetus given to scientific research, both medical and non-medical, by the war-time emergency such as resulted in the discovery of BAL. The many chemists, pharmacologists, and clinicians—far too numerous to mention all by name—who collaborated in this discovery and its important applications are surely to be congratulated on a good job well done.

W. H. B.

REVIEWS

Ambulatory Proctology. By ALFRED J. CANTOR, M.D.; foreword by BEAUMONT S. CORNELL, M.D. 524 pages; 14.3 × 20.9 cm. Paul B. Hoeber, Inc., New York, N. Y. 1946. Price, \$8.00.

The author presents a valuable discussion of the diseases of the colon, rectum and anus. As indicated in the title, the book stresses ambulatory treatment. In the opinion of the reviewer many of the procedures recommended for office practice should not be attempted outside of a hospital except perhaps by an experienced proctological surgeon with exceptional equipment and assisting personnel in his office.

T. R. A.

The Modern Treatment of Diabetes Mellitus. By WILLIAM S. COLLENS, B.S., M.D., and LOUIS C. BOAS, A.B., M.D. 514 pages; 15.5 × 23 cm. Charles C. Thomas, Springfield, Illinois. 1946. Price, \$8.50.

The authors present their book as "a practical comprehensive guide for the general practitioners who treat diabetic patients" and it contains a great deal of information on dietary and insulin therapy of the disease.

The diagnostic aspects of the disease are discussed briefly and the major portion of the book concerns itself with treatment. Diabetes mellitus is classified according to the severity of the disease, the nutritional status of the patient and the presence or absence of acidosis. Detailed descriptions of the diets to be employed for the various types of the disease with methods of calculation and clock-like diagrams showing hours of feeding and insulin administration are clearly presented. The complications are discussed under their different headings and the discussion and illustration of degenerative disease of the peripheral arteries are well presented. Thirty-five pages are devoted to laboratory procedures and technics of insulin administration. Included with the book is a Collens Diet Calculator which is intended to simplify diet-writing.

This book is a well organized presentation of the treatment of diabetes mellitus. It should prove a valuable guide to the many physicians who are faced with the multitude of problems that may arise in the treatment of this disease.

J. Z. B.

The Venereal Diseases. By JAMES MARSHALL, M.B., B.S., M.R.C.S., L.R.C.D., Major R.A.M.C., Command Venereologist to the Eastern Command and London District. 348 pages; 14.5 × 22 cm. Macmillan & Co., London. 1946. Price, \$4.50.

The author has presented his subject in a manner which does not conform to the methods used in this country. The chapters on gonorrhea give only brief mention of the necessity for cultural proof of cure, and great stress is laid on the chemotherapy of the disease, but mention of the use of penicillin is omitted. This latter omission may be due to the fact that at the time that this book was written, penicillin did not enjoy the wide use that it does at the present time. No mention is made of the necessity for routine serologic tests for syphilis in the treatment of patients for gonorrhea. The description of the course of the disease in men, women, and female children is adequate. These chapters dealing with the treatment of syphilis are now outdated due to the almost universal use of penicillin. At the time this book was written evidently mapharsen was infrequently used in Great Britain, and the author

speaks of it in disparaging terms. The subjects of chancroid, lymphogranuloma venereum, and granuloma inguinale are very briefly covered in six pages of the text. Unfortunately, this book cannot be recommended as a guide for students or practitioners in the United States.

H. M. R., JR.

The Medical Value of Psychoanalysis. By FRANZ ALEXANDER, M.D. 278 pages; 21 × 15 cm. W. W. Norton Co., Inc., New York. 1936. Price, \$3.00.

This book, by one of the leaders of psychoanalysis in this country, although published ten years ago, is still up-to-date and very timely. It will have especial appeal to those who are currently interested in psycho-somatic problems. It is written in clear, understandable language and the conclusions presented are well supported by careful studies. The content of the book concerns itself with the development, theory and implications of psychoanalysis. Extravagant claims are carefully avoided. The most useful chapter describes how recent researches have improved our understanding and treatment of such conditions as: Duodenal ulcers, gastric neurosis, mucous colitis, chronic constipation, essential hypertension and other similar problems. Many stimulating suggestions are made regarding the problems that need to be further studied. The author also makes suggestions for improving the medical student's understanding of psychogenic factors in disease.

H. W. N.

The Examination of Reflexes. A Simplification. By ROBERT WARTENBERG, M.D. Foreword by FOSTER KENNEDY, M.D. The Year Book Publishers, Inc., Chicago. 1945. 222 pages; 18.5 × 12.5 cm. Price, \$2.50.

"Again and again in my teaching," the author states, "I have been impressed by the confusion of the student as he struggles with the multitudinous reflexes and their chaotic nomenclature. These studies on reflexes were undertaken primarily with the idea of offering him a simple and comprehensive review of the reflexes in their relation to practical neurologic diagnosis. This entire study is based on and developed from a few fundamental theoretic postulations on the physiologic nature of the muscle stretch reflexes."

"The time of purely descriptive symptomatology is over," the author says at another point. "Modern neurology needs and wants more physiologic orientation. Every new observation in clinical neurology should be subjected to a strict physiologic interpretation."

These quotations sum up the purpose and the basis of the studies presented in this book. The author interprets the deep reflexes uniformly as muscle stretch reflexes. "The muscle reacts to . . . sudden stretching (through a sudden, brief concussion) with contraction, which constitutes what is called the deep, or tendon, reflex." The author distinguishes from them such reflex phenomena as associated movements, postural reflexes, support reactions. "The contraction of a muscle on being stretched may exist in latent form and become distinct, or apparent at all, only when there is a functional or an organic increase in muscle tonus." ". . . the appearance of some reflexes—usually latent—in the presence of a pyramidal lesion does not mean that the reflexes are new, but rather that they represent the pathologic exaggeration of normal reflexes which exist in latent form." This applies to such pyramidal reflexes as the Rossolimo, Troemner, Mendel-Bechterew, etc.

Many reflexes described in the literature, when considered on the basis of physiological interpretation, are identical with one another, such as the Rossolimo reflex, the Zhukovski-Kornilow, the Yoshimura reflex. They are one and the same reflex insofar as the same muscles are stimulated, even though by different methods. The

fact that one and the same reflex can be elicited from different points, was used by many investigators to claim that they had found a new reflex, which has led to great confusion in neurological nomenclature. "Since concussion of the muscle and its stretching constitute the true cause of the deep muscle reflex, the point from which this response may be achieved is not essential. It is irrelevant whether the concussion comes from the tendon, from the neighboring joints or from bone, or is obtained through a broad mass percussion of the muscle itself." "If, in interpreting and naming the reflexes, one shifts the focus of attention from the point of elicitation to the muscle whose action is provoked, an essential simplification, a better physiologic understanding and a distinct didactic advantage result."

Wartenberg does away with the distinction of tendon, bone, periosteal, osteo-periosteal, osteo-tendon, joint, fascial and aponeurotic reflexes, on the physiological basis that "the receptors of the 'tendon and periosteal' reflexes lie not in the tendon or in the periosteum but in the muscle itself." "From a neurophysiologic standpoint the tendon is, so to speak, passive, dead tissue, and no stimulation of the tendon can evoke any reflex action unless the muscle tissue is influenced through the tendon." Likewise, "the periosteum is only the point of application of the stretch stimulus." The same is true for joints, bones, etc. "These structures serve only to transmit the stretch stimulus. The deep reflexes are physiologically muscle stretch reflexes."

From the muscle stretch, or deep, reflexes, Wartenberg distinguishes the superficial, or "skin" reflexes. The stimulus is applied to the skin, without directly involving the mass of the muscle. It is a skin-muscle reflex, not a direct, but an indirect muscle reflex.

The bulk of the book consists in a detailed description of the various reflexes described in the literature, showing that many of them have different names only because described by several investigators, or because each method of elicitation of the reflex has been called a new reflex. The methods of elicitation and of reinforcement of reflexes are described, and their physiological as well as their clinical significance are discussed.

It should be obvious that clarification and simplification are indeed achieved by this approach, and the bewildering multiplicity of reflexes is reduced to a few reflex entities. One may doubt whether the author with this presentation achieves the goal of offering the student a really simple review of the reflexes in their relation to neurological diagnosis. For a review to be simple and readily understood by the medical student, the author perhaps deals too extensively with the conflicting claims of the various authors. Possibly the task of sifting the superabundant material made this unavoidable.

As an attempt to simplify and clarify neurological diagnostic procedures, and to explain their physiological and clinical significance, the book is of great practical and theoretical value. It contains a comprehensive bibliography (465 numbers), a subject and an author index.

H. W. L.

BOOKS RECEIVED

Books received during October are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Harvey Cushing. A Biography. By JOHN F. FULTON. 754 pages; 24.5 × 16 cm. 1946. Charles C. Thomas, Springfield. Price, \$5.00.

The Diagnosis and Treatment of Bronchial Asthma. By LESLIE N. GAY, M.D. Foreword by Warfield T. Longcope, M.D. 334 pages; 24 × 16 cm. 1946. Williams and Wilkins Company, Baltimore. Price, \$5.00.

- Leprosy*. Third Edition. By Sir LEONARD ROGERS, M.D., F.R.C.P., and ERNEST MUIR, M.D., F.R.C.S. 280 pages; 22 × 14.5 cm. 1946. Williams and Wilkins Company, Baltimore. Price, \$7.00.
- Treponematoses*. By ELLIS H. HUDSON, M.D. Edited by HENRY A. CHRISTIAN, F.A.C.P., F.R.C.P. 122 pages; 24 × 16 cm. 1946. Oxford University Press, New York. Price, \$2.50.
- Manual of Applied Nutrition*. Second Edition. Compiled by HELEN BAUGHMAN, KATHLEEN M. LEWIS and ELOISE R. TRESCHER. 103 pages; 19 × 13 cm. 1946. The Johns Hopkins Hospital, Baltimore. Price, \$1.50.
- Medical Uses of Soap*. A Symposium. By various authors. 195 pages; 23.5 × 15.5 cm. 1946. J. B. Lippincott Company, Philadelphia. Price, \$3.00.
- Las Neumopatías Accitosas*. Estudio Clínico y Experimental. By various authors. Edited by EL ATENEO. 128 pages; 27.5 × 18.5 cm. Librería y Editorial "El Ateneo," Buenos Aires.
- Victory Over Pain*. A History of Anesthesia. By VICTOR ROBINSON, M.D. 338 pages; 22 × 15 cm. 1946. Henry Schuman, New York. Price, \$4.00.
- The Chest*. A Handbook of Roentgen Diagnosis. By LEO G. RIGLER, M.D. 352 pages; 21 × 14 cm. 1946. Year Book Publishers, Inc., Chicago. Price, \$6.50.
- Hygiene*. Fourth Edition. By FLORENCE L. MEREDITH, B.Sc., M.D. 837 pages; 24 × 16.5 cm. 1946. The Blakiston Company, Philadelphia. Price, \$4.00.
- Mongolism and Cretinism*. By CLEMENS E. BENDA, M.D. 310 pages; 24 × 15.5 cm. 1946. Grune and Stratton, New York. Price, \$6.50.
- Essentials of Medicine*. Fifteenth Edition. By CHARLES PHILLIPS EMERSON, JR., M.D., and JANE ELIZABETH TAYLOR, R.N., B.S., M.Ed. 688 pages; 21 × 14 cm. 1946. J. B. Lippincott Company, Philadelphia. Price, \$3.50.
- A Textbook of Clinical Neurology*. Second Edition, Revised. By J. M. NIELSEN, M.D., F.A.C.P. 699 pages; 26 × 18.5 cm. 1946. Paul B. Hoeber, Inc., New York. Price, \$7.50.

COLLEGE NEWS NOTES

LIFE MEMBERS

The College takes pleasure in announcing that the following Fellows have become Life Members of the College:

Dr. Henry M. Moses, Brooklyn, N. Y., October 23, 1946
Dr. Henry L. C. Weyler, Providence, R. I., November 4, 1946
Dr. W. E. G. Lancaster, Fargo, N. D., November 14, 1946

Dr. William G. Leaman, Jr., F.A.C.P., Philadelphia, has presented to the College Library of Publications by Members a copy of "Management of Common Cardiac Conditions," published by J. B. Lippincott Co. Edited by Dr. Leaman, the book contains selected presentations from the A.C.P. postgraduate course in Cardiology which was given in Philadelphia in the spring of 1946 under Dr. Leaman's direction.

AMERICAN BOARD OF INTERNAL MEDICINE EXAMINATIONS

The American Board of Internal Medicine has announced that oral examinations will be held at Chicago, February 12, 13, and 14, 1947 (closing date, January 1, 1947); at Chicago, April 24, 25, and 26, 1947 (closing date, February 15, 1947); and at Philadelphia, June 5, 6, and 7, 1947 (closing date, April 1, 1947). The written examination will be given by the Board on March 17, 1947, instead of February 17 as had been announced earlier.

Dr. Philip Levine, F.A.C.P., Raritan, N. J., Dr. Alexander S. Wiener, F.A.C.P., Brooklyn, N. Y., and the Army Epidemiological Board, of which Dr. Francis G. Blake, F.A.C.P., New Haven, Conn., has been chairman, received Lasker Awards at the recent meetings of the American Public Health Association. The awards are made for distinguished research on problems affecting the public health.

A.C.P. RESEARCH FELLOWSHIPS

The first of the College's Research Fellowships for the year 1947-48 has been awarded by the Committee on Fellowships and Awards, Dr. Reginald Fitz, F.A.C.P., chairman, and the Board of Regents to Dr. Tom Fite Paine, Jr., Aberdeen, Miss. The fellowship will enable Dr. Paine to continue studies of infectious diseases, with especial reference to chemotherapy and the use of antibiotics, in which he is presently engaged under the supervision of Dr. Maxwell Finland, F.A.C.P., at the Thorndike Memorial Laboratory of the Boston City Hospital.

Following completion of his medical course at Vanderbilt University in 1942, Dr. Paine interned at the Strong Memorial Hospital, Rochester, N. Y. During his subsequent service in the A.U.S., Dr. Paine received an assignment to Camp Detrick, and there participated in clinical and laboratory studies of infectious diseases.

A limited number of additional research fellowships will be awarded, to begin, in most cases, July 1, 1947, and to continue in effect for one year. Their purpose is to provide an opportunity for research training in the basic medical sciences or in the application of these sciences to clinical investigation for physicians who are in the early stages of their preparation for teaching and investigative careers in internal medicine and allied fields. The stipends vary from \$1800 to \$3000 for the year, according to the applicants' needs. Application forms may be had on request to The

American College of Physicians, 4200 Pine St., Philadelphia 4, Pa. Awards will be made on or about January 1, 1947; applications should be submitted as early as is possible.

A.C.P. REGIONAL MEETING, MEMPHIS

A Regional Meeting of the College for Arkansas, Louisiana, Mississippi, Tennessee and Texas was held at Memphis, November 22, through the coöperation of Governors Oliver C. Melson, Edgar Hull, John Archer, William C. Chaney and M. D. Levy. A feature of the meeting was the dinner in honor of Dr. Hugh J. Morgan, President-Elect of the College.

The scientific program was as follows:

1. Coronary Artery Disease,
William D. Stroud, M.D., F.A.C.P., Philadelphia.
2. Clinical Pathologic Conference,
Conley H. Sanford, M.D., F.A.C.P., William C. Colbert, M.D., F.A.C.P.,
and Douglas H. Sprunt, M.D., F.A.C.P., Memphis.
3. New Knowledge in the Treatment of Malaria,
H. Packer, M.D., Memphis.
4. Treatment of Intractable Peptic Ulcer,
Walter L. Palmer, M.D., F.A.C.P., Chicago.
5. Hypertension,
Hugh J. Morgan, M.D., F.A.C.P., Nashville.

Dr. Leonard G. Rowntree, F.A.C.P., Philadelphia, Pa., and Miami, Fla., has been presented with the Medal for Merit. The citation reads, in part: "as chief of the medical division of the Selective Service System from Dec. 18, 1940 to June 16, 1945 (he) anticipated, met and solved, with never failing diligence and professional proficiency, the ever changing medical problems which arose in the administration of the Selective Service System. . . . He merits the gratitude of the nation for his immense contributions to the mobilization of its manpower."

Dr. Lucian A. Smith, F.A.C.P., Rochester, Minn., is the recipient of the Bronze Star for his development of "a method for early diagnosis and effective therapy of various types of dysenteries." Dr. Smith's cited achievements were accomplished while he was on duty in the Medical Corps, A.U.S., in New Guinea in 1944-45.

In recognition of the forty years of distinguished service which Dr. Berthold S. Pollak, F.A.C.P., Jersey City, N. J., has rendered as Medical Director of the Hudson County Tuberculosis Hospital and Sanatorium, the county's Board of Chosen Freeholders took action on October 10, 1946, to change the name of the hospital to The Berthold S. Pollak Hospital for Chest Diseases.

AMERICAN TRUDEAU SOCIETY COURSE

A postgraduate course in Thoracic Diseases will be given at the University of Wisconsin Medical School, Madison, March 3-8, 1947, under the sponsorship of The American Trudeau Society. The registration is limited to thirty qualified physicians; priority will be given to residents of midwestern states. The fee is \$50. A prospectus of the course and application forms may be secured from Cameron St. C.

Guild, M.D., Executive Secretary, The American Trudeau Society, 1790 Broadway, New York 19, N. Y.

A course in Electrocardiographic Interpretation for *graduate physicians* will be given at the Michael Reese Hospital Postgraduate School by Dr. Louis N. Katz, Director of Cardiovascular Research. The class will meet each Wednesday from 7:00 to 9:00 p.m., for twelve weeks, beginning February 12.

Further information and a copy of the lecture schedule may be obtained upon application to the Office of the Dean, Michael Reese Hospital Postgraduate School.

RETIREMENTS FROM SERVICE

Since the last publication of this journal, the following members of the College have been reported retired or on terminal leave (to November 12, 1946 inclusive)..

Francis J. Braceland, Chicago, Ill. (Capt., MC, USNR)
 Joseph E. Brackley, Boston, Mass. (Major, MC, AUS)
 Joseph L. Campbell, Ulster, Pa. (Lt. Col., MC, AUS)
 George D. Chunn, Sarasota, Fla. (Col., MC, USA)
 Joseph H. Delaney, Columbia, Mo. (Major, MC, AUS)
 Frank S. Dietrich, Portland, Ore. (Lt. Col., MC, AUS)
 Mackinnon Ellis, Bryn Mawr, Pa. (Comdr., MC, USNR)
 Waldo B. Farnum, New York, N. Y. (Col., MC, AUS)
 Ralph M. Fellows, Milwaukee, Wis. (Lt. Comdr., MC, USNR)
 Kenneth G. Gould, Tampa, Fla. (Col., MC, USA)
 Marshall W. Graham, Washington, Pa. (Lt. Comdr., MC, USNR)
 Milton E. Hubbard, Los Angeles, Calif. (Col., MC, AUS)
 Saul Jarcho, New York, N. Y. (Lt. Col., MC, AUS)
 Emory H. Main, Philippi, W. Va. (Capt., MC, AUS)
 Hugo Mella, Washington, D. C. (Col., MC, AUS)
 Frank L. Price, Youngstown, Ohio (Lt. Comdr., USPHS)
 Norman Reider, Los Angeles, Calif. (Major, MC, AUS)
 Lee Rice, San Antonio, Tex. (Col., MC, AUS)
 Paul Richmond, Jr., Worcester, Mass. (Capt., MC, USN)
 Joseph H. Shaffer, Detroit, Mich. (Lt. Col., MC, AUS)
 Ralph K. Shields, Bethlehem, Pa. (Major, MC, AUS)
 Oliver C. Wenger, Washington, D. C. (Sr. Surgeon, USPHS)
 Edward C. White, Alexandria, Va. (Rear Admiral, MC, USN)

AMERICAN COLLEGE OF PHYSICIANS POSTGRADUATE COURSES.

No other activity of the American College of Physicians has met with greater enthusiastic support than that of its postgraduate courses. The demand greatly exceeds available facilities. These courses are looked upon as superior to any other work of the kind available in this country, and other groups have started to imitate our work. During 1946 the College organized twenty-three separate and distinct courses, ten during the Spring and thirteen during the autumn, with a registration in excess of 1200 physicians, chiefly Fellows and Associates of the College.

Many of the courses were oversubscribed.

The Spring, 1947 Schedule

The following list of courses are scheduled during the winter and spring of 1947. The Postgraduate Bulletin will be published on or about January 1, 1947, and will be

distributed to all Fellows and Associates of the College and to such other physicians as have requested that their names be placed on the mailing list. Reservations may be made in advance by communicating with E. R. Loveland, Executive Secretary, American College of Physicians, 4200 Pine St., Philadelphia, 4, Pa.

GROWTH, ISOTOPES, AND TUMOR FORMATION.

The Lankenau Hospital Research Institute and The Institute for Cancer Research, Philadelphia, Pa.

Stanley P. Reimann, M.D., F.A.C.P., Director.

February 3-8, 1947.

Fee: A.C.P. Members, \$40.00; Non-Members, \$80.00.

CARDIOVASCULAR DISEASE.

University of Southern California, Los Angeles, Calif.

George C. Griffith, M.D., F.A.C.P., Director.

February 3-7, 1947.

Fee: A.C.P. Members, \$20.00; Non-Members, \$40.00.

ARTHRITIS AND ALLIED CONDITIONS.

Mayo Foundation, University of Minnesota, Rochester, Minn.

Philip S. Hench, M.D., F.A.C.P., Director.

One week—March 24-29, 1947.

Fee: A.C.P. Members, \$20.00; Non-Members, \$40.00.

PERIPHERAL VASCULAR DISEASE.

Mayo Foundation, University of Minnesota, Rochester, Minn.

Edgar V. Allen, M.D., F.A.C.P., Director.

One week—March 17-22, 1947.

Fee: A.C.P. Members, \$20.00; Non-Members, \$40.00.

CARDIOVASCULAR DISEASE.

Emory University School of Medicine, Atlanta, Ga.

Bruce Logue, M.D., F.A.C.P., Director.

March 31-April 5, 1947.

Fee: A.C.P. Members, \$20.00; Non-Members, \$40.00.

INTERNAL MEDICINE.

University of Michigan Medical School, Ann Arbor, Mich.

Cyrus C. Strugis, M.D., F.A.C.P., Director.

April 7-19, 1947.

Fee: A.C.P. Members, \$40.00; Non-Members, \$80.00.

CARDIOVASCULAR DISEASE.

Northwestern University Medical School, Chicago, Ill.

J. Roscoe Miller, M.D., F.A.C.P., Director.

April 21-26, 1947.

Fee: A.C.P. Members, \$20.00; Non-Members, \$40.00.

CARDIOVASCULAR DISEASE.

Philadelphia General Hospital.

Francis C. Wood, M.D., F.A.C.P., and Calvin F. Kay, M.D., Directors.

One week—May 12-17, 1947.

Fee: A.C.P. Members, \$20.00; Non-Members, \$40.00.

INTERNAL MEDICINE, WITH EMPHASIS UPON NUTRITION AND METABOLISM.
 University of Cincinnati College of Medicine, Cincinnati, Ohio.
 Marion A. Blankenhorn, M.D., F.A.C.P., Director.
 May 26–June 7, 1947.
 Fee: A.C.P. Members, \$40.00; Non-Members, \$80.00.

28TH ANNUAL SESSION, A.C.P.

Chicago, Ill. (Headquarters: Palmer House).
 David P. Barr, M.D., F.A.C.P., President.
 LeRoy H. Sloan, M.D., F.A.C.P., General Chairman.
 April 28–May 2, 1947.
 Fee: A.C.P. Members, free; Non-Members, \$15.00.

Detailed Outline

COURSE No. 1—GROWTH, ISOTOPES, AND TUMOR FORMATION

(February 3–8, 1947)

The Lankenau Hospital Research Institute and The Institute for Cancer Research
Philadelphia, Pa.

STANLEY P. REIMANN, M.D., F.A.C.P., *Director*
 (Minimal Registration, 15; Maximal Registration, 30)

Fees: A.C.P. Members, \$40.00
 Non-Members, \$80.00

Officers of Instruction

Oscar V. Batson, M.D., Professor of Anatomy, University of Pennsylvania Graduate School of Medicine.

Philip D. Bonnet, M.D., Director, The Lankenau Hospital.

Edward L. Bortz, M.D., F.A.C.P., Chief of Medical Service B, The Lankenau Hospital.

Robert Briggs, Ph.D., Department of Experimental Embryology, The Lankenau Hospital Research Institute.

Charles L. Brown, M.D., F.A.C.P., Dean, Hahnemann Medical College and Hospital of Philadelphia.

Clark E. Brown, M.D., Pathologist, The Lankenau Hospital.

Hugh J. Creech, Ph.D., Immuno-Chemist, Department of Immunity, The Lankenau Hospital Research Institute.

Lawrence Curtis, M.D., Associate Professor of Oral Surgery, University of Pennsylvania Graduate School of Medicine.

Earl A. Daugherty, M.D., F.A.C.P., Assistant Physician, The Lankenau Hospital.

J. Montgomery Deaver, M.D., F.A.C.S., Chief of Surgical Service A, The Lankenau Hospital.

- Irene C. Diller, Ph.D., Cytologist, Department of Cytology, The Lankenau Hospital Research Institute.
- Gilson Colby Engel, M.D., F.A.C.S., Chief of Surgical Service B, The Lankenau Hospital.
- Elizabeth U. Green, Ph.D., Experimental Embryologist, The Lankenau Hospital Research Institute.
- Mary A. Hamilton, Ph.D., Immuno-Chemist, The Lankenau Hospital Research Institute.
- Fred L. Hartmann, M.D., Chief of Medical Service A, The Lankenau Hospital.
- Theodore S. Hauschka, Ph.D., Micro-Biologist, The Lankenau Hospital Research Institute.
- John Kidd, M.D., Professor of Pathology, Cornell University Medical College, New York, N. Y.
- Theodore F. Lavine, Ph.D., Organic Chemist, The Lankenau Hospital Research Institute.
- William G. Leaman, Jr., M.D., F.A.C.P., Professor of Medicine, Woman's Medical College of Pennsylvania.
- Warren H. Lewis, M.D., Wistar Institute of Anatomy, Philadelphia, Pa.
- L. G. Livingston, Ph.D., Assistant Professor of Botany, Swarthmore College; Plant Physiologist, The Lankenau Hospital Research Institute.
- Hans May, M.D., Assistant, Surgical Service B, The Lankenau Hospital; Assistant Professor of Surgical Pathology, University of Pennsylvania Graduate School of Medicine.
- Jane R. McConnell, Ph.D., General Physiologist, The Lankenau Hospital Research Institute.
- Grace Medes, Ph.D., Physiological Chemist, In Charge of Isotope Research, The Lankenau Hospital Research Institute.
- Valy Menkin, M.D., Professor of Experimental Pathology, Temple University School of Medicine.
- Malcolm W. Miller, M.D., F.A.C.P., Assistant Physician, The Lankenau Hospital.
- Francis Ashley Montagu, M.D., Fellow of The Royal Anthropological Society of Italy; Staff Member, The American Museum of Natural History.
- Jesse T. Nicholson, M.D., F.A.C.S., Professor of Orthopedic Surgery, University of Pennsylvania Graduate School of Medicine.
- Jane Oppenheimer, Ph.D., Assistant Professor of Biology, Bryn Mawr College.
- Henry F. Page, Jr., M.D., F.A.C.P., Assistant Physician, The Lankenau Hospital.
- Daniel B. Pierson, Jr., M.D., F.A.C.P., Assistant Physician, The Lankenau Hospital.
- Allen Reid, Ph.D., Physical Chemist in Charge of Construction C-13 Plant, Sun Oil Company, Marcus Hook, Pa.
- Hobart A. Reimann, M.D., F.A.C.P., Professor of Medicine, Jefferson Medical College of Philadelphia.
- Stanley P. Reimann, M.D., F.A.C.P., Director, The Lankenau Hospital Research Institute and the Institute of Cancer Research; Associate Professor of Surgical Pathology, University of Pennsylvania Graduate School of Medicine; Professor of Oncology, Hahnemann Medical College and Hospital of Philadelphia; Chairman, Cancer Commission, Pennsylvania State Medical Society.
- Jack Schultz, Ph.D., Department of Genetics, The Lankenau Hospital Research Institute.
- R. R. Spencer, M.D., National Cancer Institute, Bethesda, Md.
- Gerrit Toennies, Ph.D., Organic Chemist, The Lankenau Hospital Research Institute.
- Charles A. W. Uhle, M.D., Urologist, The Lankenau Hospital.

Sidney Weinhouse, Ph.D., Organic Chemist, Houdry Process Corporation, Marcus Hook, Pa.

Philip R. White, Ph.D., Department of General Physiology, The Lankenau Hospital Research Institute.

General Statement

An advanced course designed to present the basic problems of growth and their application to various practical problems in medicine, such as physique, constitution, wound healing, regeneration, inflammation, congenital anomalies, and tumor formation. In this course medicine will be regarded as a branch of biology.

Beginning this subject, the basic factors will be presented by biologists and others in the fundamental field. The practical applications will then be considered and emphasized together with the problems presented in clinical practice.

The introduction of isotopes as tracers in studies of intermediary metabolism has been revolutionary. As in many other fields, isotopes as tracers have contributed knowledge to the growth problem. A whole day session will be devoted to isotopes—how they are used as tracers, what teams must be organized for their proper use, and the instruments for their measurement.

In the morning physicists will present the highlights of newer knowledge of the atom; biochemists will present results in special fields thus far opened. In the afternoon, a special trip has been arranged to the Houdry Process Corporation and the Sun Oil Company plants in Marcus Hook, a few miles south of Philadelphia. At these plants the apparatus for the preparation of stable isotopes, and the instruments for measuring them, as well as radioactive isotopes, will be inspected and demonstrated.

A morning session will be devoted to the biological problems of cancer. They will be discussed in a session devoted to this subject with a final paper on "Survival Time" by R. R. Spencer, M.D., of the National Cancer Institute. Finally, specific tumors will be presented and methods of diagnosis, treatment, and general management will be stressed.

Morning Meetings: The Lankenau Hospital Nurses Training School Auditorium
22nd St. & Girard Ave.

Afternoon Meetings: The Laboratory of The Lankenau Hospital Research Institute

Outline of Course

Monday, February 3.

Presiding: Dr. Bortz.

Growth is cyclical and is compounded of numerous separable processes each with its own set of starting, stimulating, regulating, inhibiting factors.

Differential growth—the various types of human beings determined by both heredity and environment. Classification of types, their strengths and weaknesses.

The establishment of growth patterns in early life as a basis for normal development.

The human constitution and its various patterns as related to particular disease states will be discussed.

A.M. Session.

9:00 Greetings and Introductory Remarks.

Officials of Hospital, Institute and The American College of Physicians.

- 9:30 Cycles of Growth.
Dr. Stanley P. Reimann.
- 10:00 The Varieties of Man and the Problems of Growth.
Dr. Montagu.
- 10:30 Normal and Pathologic Growth Patterns.
Dr. Batson.
- 11:15 Constitution and Disease.
Dr. Hobart A. Reimann.
- 12:30 LUNCHEON with members of Research and Hospital Staff.
- P.M. Session
- 2:00 Demonstrations and Conferences: (See descriptions) 1, 2, 3, 4, 5, 6, 7, 8, 9, 10.
- 5:30 Cocktails—Library of The Research Institute.
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Demonstrations and Conferences

Three afternoons will be devoted to demonstrations and conferences. The students will be divided into small units, and each group will be assigned to a particular demonstration. The following problems will be taken up:

1. Special nutritional requirements for growth.
Dr. Bonnet. Significance of sulfur linkages, the methyl group. Intestinal and liver factors involved.
2. Cancer and protozoa.
Dr. Hauschka and Group. Experiments with trypanosomes and their products in mouse tumors. Specific tissue inhibitors such as hexenolactone.
3. The use of tissue cultures as a means of solving problem of growth.
Dr. McConnell and Group. Attempts to devise chemically known culture media. The effects of bacterial polysaccharide, emetin, hexenolactone and other substances on cell viability.
4. Proteins in cancer.
Drs. Toennies, Lavine and Group. Possibilities of differentiation from proteins in normal tissue. Properties of the amino acids and methods for their chemical and bio-assay. Newer findings in amino acid linkages and transmutations.
5. Immunity to carcinogens and to cancer itself.
Drs. Creech and Hamilton. The production of antisera and anti-antisera to the bacterial polysaccharide used in treatment of human sarcoma. Why antisera are necessary.
6. Cultures of both normal and cancerous plant tissues.
Dr. White and Group. A discussion of the usefulness in helping to solve problems in animal growth. What is learned from cancerous plant tissues in relation to abnormal human growths.
7. The control of differentiation as a prerequisite to a fundamental knowledge of the physiology of the cancer cell.
Drs. Briggs, Green and Group. Tumors in tadpoles. Nuclear transplantations. Production of rhabdomyosarcomas in mice. Possible viral etiology.
8. Methods for studying human chromosomes.
Dr. Schultz and Group. Chromosomes and genes. Their study by cytological, genetic, and chemical methods. The beginnings of a map of human chromosomes. The apparatus and technic of microchemical studies of enzyme activity.

9. Isotopes in metabolic studies.

Dr. Medes and Group. Methods of testing in whole animals, organs, tissue slices, tissue brei. What to look forward to when Isotopes become available in quantity for human study. How to organize a "Team" for this work.

10. The effect of *B. prodigiosis* polysaccharide and other agents on tumorous growths.

Dr. Diller and Group. The effect on mouse and human tumors. The hemorrhage and necrosis. The synergistic effect of x-rays and polysaccharide. The use of adrenal cortical extract with and without polysaccharide. The cytological details of cells in mitosis being destroyed.

Tuesday, February 4.

Presiding: Dr. Pierson.

Wound healing is compounded of proliferation, differentiation and organization of cells into tissues. Cell movements singly and en masse are necessary. The factors, local and general, stimulating and inhibiting these processes.

Inflammation and repair—Newer findings in capillary participation, fluid exchange, lymphatic drainage and their effect on repair.

Convalescence and regeneration—Factors which accelerate or impede convalescence and regeneration.

Transplantation of tissues, of organs, homoplastic, heteroplastic. Factors influencing. Transplantation of tumors. Their significance and value as test objects.

Reconstructive surgery—Principles; Illustrated by examples from various parts of the body.

A.M. Session.

9:30 Wound Healing and Its Cellular Physiology.
Dr. Lewis.

10:00 Inflammation and Repair.
Dr. Menkin.

10:30 Convalescence and Régénération.
Dr. Charles L. Brown.

11:00 The Biological Background of Transplantation.
Dr. Briggs.

11:30 Applications of Wound Healing and Transplantation to Reconstructive Surgery.
Dr. May.

LUNCHEON

P.M. Session

2:00 Demonstrations.

3:00-5:00 Discussion of Demonstrations.

Wednesday, February 5.

Presiding: Dr. Miller.

Until recently growth anomalies were described anatomically. In modern investigations physiological and chemical explanations have been added. For example, Spemann's organizer phenomena. Chemical substances as too much calcium may cause anomalies. Infections such as German measles may lead to anomalies. Transplantation experiments have clarified genic and environmental factors to a considerable degree. The three germ layers are no longer valid. Human beings have regulatory

eggs as demonstrated among others by the Dionne quintuplets which are from one ovum, etc.

Head and neck—Hare lip, cleft palate, strabismus, ectopic salivary glands, thyroid, branchiogenic cysts and solid tumors, thyrohyoid ducts, etc., etc.

Cardiac anomalies—Some are compatible with long life, others with shortened life, some die at birth or before. The hereditary background. Certain operative procedures can be done as e.g., patent ductus arteriosus.

Urogenital—Horse shoe kidneys, double ureters, extrophia of bladder, undescended testes, etc. Diagnosis and treatment.

Extremities—Club feet, dislocation hip, short arm, etc.

A.M. Session

9:30 Physiological Causes of Growth Anomalies.

Dr. Oppenheimer.

10:30 Growth Anomalies of the Head and Neck; Their Diagnosis and Treatment.

Dr. Curtis.

11:00 Cardiac Anomalies and Life Expectancy.

Dr. Leaman.

11:30 Growth Anomalies of the Urogenital System; Their Diagnosis and Treatment.

Dr. Uhle.

12:00 M. Growth Anomalies of the Extremities and Their Correction.

Dr. Nicholson.

LUNCHEON

P.M. Session

2:00 Demonstrations.

3:30–5:00 Discussion of Demonstration Material.

Thursday, February 6.

Presiding: Dr. Daugherty.

Theory of isotopes—Present day conception of the structure of the atom. The transmutability of elements. Radioactive and stable isotopes. Choice for various problems.

Methods of separation and analysis—The thermal diffusion and chemical methods of separation of stable isotopes. Methods of making radioactive isotopes. The mass spectrograph and the Geiger-Muller Counter.

Biological production—Methods of making by biological means the necessary compounds containing isotopes for human and animal work.

Fat metabolism—The use of heavy carbon for the study of fat metabolism. How fats are metabolized.

A.M. Session.

9:30 Theory of Isotopes.

Dr. Weinhouse.

10:00 The Preparation and Analysis of Isotopes.

Dr. Reid.

11:00 The Biological Production of Compounds.

Dr. Livingston.

12:00 M. Studies in Fat Metabolism with Isotope Tracer.

Dr. Medes.

LUNCHEON

Afternoon: Visit to Houdry Process Corporation's Laboratory and Sun Oil Company Plant, Marcus Hook, Pa., to inspect apparatus for separating heavy carbon and instruments for measuring quantitatively both stable and radioactive isotopes. They are:

Thermal Diffusion Plants
Chemical Separation Plants
Mass Spectrograph
Geiger-Muller Counters.

Friday, February 7.

Presiding: Dr. Page.

Differentiation—The most important process leading to the different kinds of cells, tissues and organs; species specificity. Deviation of differentiation leads to tumors, benign and malignant, as well as to all other kinds of growth aberrations.

Chemical factors—The carcinogens. Immunity to conjugated products.

Genetic factors—The relation of cellular and organism inheritance to the predisposition to cancer.

Viruses and virus-like agents—Relation to special tumors and their relationship to tumor formations.

A discussion of "Survival Time" of lower species and the significance to human observations.

A.M. Session.

9:30 THE BIOLOGY OF TUMOR FORMATION.

The Problem of Cellular and Tissue Differentiation.

Dr. White.

Chemical Factors.

Dr. Creech.

Genetic Factors.

Dr. Schultz.

Viruses and Virus-like Agents.

Dr. Kidd.

STUDIES OF SURVIVAL.

Dr. Spencer.

REGIONAL MEETING, AMERICAN COLLEGE OF PHYSICIANS

P.M.

1:00 Luncheon Buffet—Headquarters of the College, 4200 Pine St., Philadelphia, Pa.

2:30 Scientific Program.

Ballroom, Warwick Hotel, 17th & Sansom Sts.

6:00 Reception.

Mezzanine, Warwick Hotel.

6:45 Dinner.

Mirror Room, Warwick Hotel.

After Dinner Program.

Edward L. Bortz, M.D., F.A.C.P., Toastmaster.

Introduction of Distinguished Guests.

Music by the Orpheus Club Male Octette.

Saturday, February 8. .

Presiding: Dr. Bonnet.

A.M. Session.

- 9:30 Cancer of the Stomach.
Dr. Engel.
- 10:00 Cancer of the Colon.
Dr. Deaver.
- 10:30 The Leukemias.
Dr. Hartmann.
- 11:00 Peculiarities of Fibrosarcoma.
Dr. Clark E. Brown.
- 11:30 General Summary.
Dr. Reimann.

OBITUARIES

DR. JAMES DEACON BRUCE

James Deacon Bruce died at Ann Arbor, Michigan, on September 5, 1946, of cerebral hemorrhage. He was born at Blackstock, Ontario, on October 4, 1872, of Scotch-Irish ancestry, and named for his mother's favorite brother, Colonel James Deacon, born in Dublin, then with the Imperial Army in India. As a descendant of Adelme de Brus, the Normans of William the Conqueror, and the Scotch Highlanders of the Eleventh Century, he embodied the qualities of his Celtic-Anglo-Norman heritage. Conservative in action, strong in convictions, and intrepid in planning, his career followed the true course of his ancestry.



JAMES DEACON BRUCE

At the Detroit College of Medicine, which he entered in 1893, he earned his way by playing professional soccer and working in the office of Dr. Preston Hickey. On May 26, 1904, he was married to Grace Campbell, a loyal and intrepid Scotswoman, who survives him. Beginning practice in a small village, Dr. Bruce encountered the usual difficult situations common to the practice of medicine in those days. Ever resourceful, he made use of the measures at hand to care for the sick or protect the well. On one occasion, in 1898, he protected the inhabitants during an epidemic of smallpox by stretching barbed wire across all roads leading into the township.

In 1904 he came to the University of Michigan Medical School for post-graduate study and spent two years in the medical department under Dr. George Dock, Dr. David Cowie, and Dr. Hugo A. Freund. Following this period of study, Dr. and Mrs. Bruce located in Saginaw where they lived until 1925. Here Dr. Bruce practiced both medicine and surgery and attained distinction as a surgeon.

During World War I, Dr. Bruce joined the Canadian Army in early 1916, served as captain in the medical corps, and was chief of the medical service at the Duchess of Connaught Hospital near London. When we entered the war, he transferred to the United States Army Medical Corps, joining the Grand Rapids Unit at Camp MacPherson, Atlanta, Georgia, and went to France in March, 1918, to serve in evacuation hospital No. 5, at Auteuil, where his ability as an administrator and director quadrupled the capacity of the hospital.

One of his experiences during his military service is recalled. He was sent on an inspection trip to Ireland. While on ward rounds at the hospital in Dublin Castle, he was shown a soldier with an unhealed, painful shrapnel wound of the thigh, which had not been immobilized in a cast. In the presence of the resident staff, the chief surgeon of the hospital said ironically, "Major Bruce, as an American officer inspecting our methods of practice, no doubt you have an opinion about the care of this case." To this Dr. Bruce replied. "Colonel, you do not have to ask me for an opinion. Simply glance at the inscription above the door of this ward." The inscription was "Rest and Pain" by James Hilton.

Soon after he returned to private practice in Saginaw, he was chosen as councilor of the Michigan State Medical Society. He served in this capacity from 1923 to 1934. This experience seemed to have crystallized certain principles, and during his official association with the Society, his efforts were thenceforth directed towards the improvement of the *quality* of medical service. Recognizing also that the cost and distribution were factors affecting the standards of medical service, he exerted every effort to develop a common understanding in formulating plans to meet these problems by a constantly improving quality of medical service.

In 1925, Dr. Bruce discontinued private practice, including surgery, and removed to Ann Arbor where he became Director of the Department of Medicine at the University of Michigan Medical School.

Two years later, upon petition of the Council of the State Medical Society to the University Regents, he was made Director of a newly created Department of Postgraduate Medicine. He consistently refused a professorial rank because, I think, there was no available professorship of "People working together for an Ideal." Observations made in practice concerning the need for the continuing education of the physician and his conviction that the future course of the medical profession would be identified with the quality of its service were the motives that impelled him to develop an educational program for the benefit of medical graduates. It was hoped to make each community as self-sufficient as possible with respect to health and medical service by postgraduate study and the improvement of community hospital teaching facilities.

Convinced that a graduate need was being neglected by educational leaders and that the *obligation of any university faculty to its students does not end with the granting of a degree*, Dr. Bruce spared no effort to bridge the gap between the classroom, the laboratory, and the application of newer knowledge to daily life. During fifteen years of service in charge of medical postgraduate education at the University of Michigan, he created and supervised a program designed to reach physicians in every community. With the full coöperation of the local physicians, modern hospital buildings and adequate laboratory facilities were provided by the Couzens' Children's Fund at Marquette and Traverse City, manned by University staff members under his stimulus, and dedicated to improvement of medical care of children by the extension of educational opportunities to the physicians of the local areas. *No such development of medical care and postgraduate and graduate training had ever been seen before in America.*

Dr. Bruce was made a Fellow of the American College of Physicians in 1925, was elected its Governor for Michigan in 1930 and in 1936 was elected to its Board of Regents. In 1939 he was elected President-Elect and served as President, 1940-1941. He was again returned to the Board of Regents in 1941 and served until 1946. He exerted a real influence in the decision for the College to acquire its present home at 4200 Pine Street, Philadelphia. During a debate among Regents and Governors of the College at the Annual Session of the College in Detroit in 1936, when opinion upon the acquiring of a College home was divided, his summary of the needs and desirability of an adequate and dignified College Headquarters unified the opinions of all present and resulted in an unanimous vote in favor of the project, to the everlasting approval and satisfaction of all members thereafter.

One of the last acts of Dr. Bruce before his death was the outright gift of \$10,000.00 to the American College of Physicians, \$5,000.00 for the establishment of a periodic Service Award in memory of the late Dr. Alfred Stengel, who in the middle 20's was responsible for widespread reorganization and reforms in the College and who had a great influence on building the College as it is known today; and \$5,000.00 for the establishment of a Lectureship in preventive medicine. The Board of Regents thereupon estab-

lished "The James D. Bruce Fund" and designated the latter part of the bequest as "The James D. Bruce Lectureship in Preventive Medicine." Furthermore, Dr. Bruce designated the American College of Physicians as one of the chief legatees under his will.

Dr. Bruce, while deeply interested in every activity of the College, probably made his greatest contribution to the growth and increasing influence of the College through the development of an educational program. Indeed, the policy of the College with respect to its ultimate function in American medicine was greatly stimulated by Dr. Bruce in his address upon being inducted into the Presidency in 1940; when he said: "The College has assumed certain obligations which include the establishment of programs of education designed to keep our members at desirable levels of proficiency, the organization of resources to permit worthy candidates to prepare themselves to be accredited by the Board of Internal Medicine, and membership in the College, and the encouragement and support of research. The effective integration of all these functions justifies our use of the term 'college'." How much this "integration of resources" (wherever they may be found) has meant to us during the postwar period!

The ideals inspired by experiences in medical graduate education were soon to be applied by integration and expansion of the available resources of the University of Michigan in more general graduate and postgraduate education. In 1931 Dr. Bruce was appointed Vice-President in Charge of University Relations at the University of Michigan. In his request to Dr. Bruce to accept this position, President Ruthven said in behalf of the University Regents and himself, "We would like frankly to adopt the policy that the University should elaborate postgraduate study service, and institutional coöperation, and we want a man to direct these activities in a large way. The movement of adult education is really revolutionary and challenges the imagination."

The attraction of this position was chiefly that it gave opportunity to correlate various educational units of the state according to their functions and relations with the world outside the campus. The Division of Health Sciences and the Division of Extramural Services were organized. The extramural teaching activities were greatly increased, and a building in Detroit was constructed to be used jointly by the Detroit Engineering Society and the University for its extramural teaching program.

An important point is that *All* teachers in the state, regardless of college affiliations, were utilized in a plan for education toward better citizenship. Rivalry between schools yielded to reason when the United States was fast losing its democratic form of government. Following the principles of Jefferson, Monroe, and Madison, laid down at Red Gap, Virginia, he discerned that education for leadership in the *forms of Anglo-Saxon democracy* would be the only method of saving it, and that universities held chief responsibility. Dr. Bruce was able to bring all state organizations into a

common working agreement toward the objective of preserving a democratic government by means of adult education.

In general, Dr. Bruce examined the educational field in relation to a hereditarily determined background, in conformity with human nature, and without pedagogical prospectus. He presented to the educational system of our country the viewpoint that medieval intramural scholasticism was not conducive either to intellectual or political freedom and that the concepts of Anglo-Saxon democracy depended upon a continuing of extramural opportunity.

After his retirement from the University at the age of seventy years, Dr. Bruce devoted much of his time to the direction of a statewide program of adult education. He served as President of the Michigan Council on Adult Education from 1941 to 1944.

As an expression of his interests, and of the demands upon his time, a few of his organizational interests are mentioned:

Vice-President in Charge of University Relations, 1931-42; Member of Executive Committee of the University Medical School, 1930-42; Medical Adviser to the University Health Service, 1925-42; Chairman, Division of Health Sciences, 1935-42; Chairman, Division of Extramural Services, 1936-42; Medical Advisory Committee of National Committee on Economic Security, Member, 1934; National Research Council, Division of Medical Sciences, Committee on Medicine, Member, 1940-42; National Commission on Graduate Medical Education, Member, 1937-40; Associated States Postgraduate Committee, Chairman, 1937-40 and 1941-; Michigan Tuberculosis Sanatorium Commission, Member, 1932-; Michigan Council on Adult Education, President, 1941-; Michigan Committee on Juvenile Delinquency, Member, 1943-; Michigan Adult Education Advisory Committee, Member, 1944-.

In his personal relationships, Dr. Bruce was gracious, kindly, and companionable. His chief diversions were the English classics, especially Goldsmith, golf, and a consuming interest in horses. He was an inspiration to those who worked with him, and while skilled in knowledge of the frailties of human nature and unexcelled as a true physician, he was a fearless defender of the principles and ideals of western civilization. Intellectually honest and courageous he never compromised a fundamental principle, and injustice was especially not tolerated. *One characteristic we can all emulate was his ability to persuade men to work together toward an ideal.*

H. H. RIECKER, M.D., F.A.C.P.

DR. GEORGE THOMAS TWYMAN

George Thomas Twyman, Independence, Mo.; born at Independence, Mo., March 22, 1888; A.B., 1913, University of Kansas; M.D., 1915, Rush Medical College, Chicago; for many years attending physician, Independence

Sanitarium and Hospital; member of courtesy staff, Research, St. Joseph and Menorah Hospitals; member, Jackson County Medical Society, Missouri State Medical Society, American Medical Association and a Fellow of the American College of Physicians since 1931; died, October 4, 1946, at the Independence Sanitarium and Hospital of diabetes mellitus and cardiac failure.

Dr. Twyman was known for his qualities of leadership and fairness and set an example in his community for his fellow-physicians to imitate. Familiarly known as Dr. Tom, he was tall, handsome with a magnetic personality. Like his father, he was the leading physician in Independence and his passing was a personal loss to many.

RALPH KINSELLA, M.D., F.A.C.P.,
Governor for Missouri

DR. ARA NATHANIEL SARGENT

Ara Nathaniel Sargent, Salem, Massachusetts, born December 30, 1867; M.D. 1893, Harvard University Medical School; served many years on the staff of the Salem Hospital; Associate of the American College of Physicians since 1920 by virtue of membership in the American Congress of Internal Medicine; died at the Salem Hospital, August 26, 1946, at the age of seventy-eight.

Dr. Sargent was considered a very valuable consultant in internal medicine in his community, and was the father of the Salem Hospital laboratory. For many years he took entire charge of it and continued his interest in an active way up to the time a resident pathologist was appointed. He was the first physician in Salem to own a blood pressure apparatus and a blood counting chamber, both of which he brought from Europe about 1904.

His judgment and sound advice were much sought after by the physicians in Salem. He always took a great interest in the training school for nurses, and for a long time taught them their laboratory work and their courses in medicine. This interest in the nursing profession he activated in his will, inasmuch as he left a certain sum of money for a scholarship fund for nurses, another fund for books for the nurses' library, and a sum for the nurses' alumnae fund. He did not forget their enjoyment, and left a small fund to maintain their parties at Christmas time.

Dr. Sargent never married, and never went about in society, but he was very fond of travel. He made many trips to Europe, to the West coast, to the Caribbean Sea and to the West Indies. His hobby was collecting fine watches and instruments of precision, such as barometers. He had a large fund of general knowledge, and was particularly versed in the knowledge of precious stones and was often consulted as to their value.

He was a man who was highly respected and admired in his community, and his contributions to the Salem Hospital were very outstanding. He

will be remembered by all his colleagues and friends as one of the outstanding physicians in his community during his life.

CHESTER S. KEEFER, M.D., F.A.C.P.,
Governor for Massachusetts

DR. ANDERS FRICK

Dr. Anders Frick, F.A.C.P., Chicago, Illinois, was born in Malmoe, Sweden, January 12, 1868. He attended Malmoe Gymnasium and the University of Lund and received his Degree of Doctor of Medicine from the Karolinan Medical and Surgical Institute (Stockholm, Sweden) in 1896. Soon after receiving his degree, he migrated to this country and began practicing on the North Side of Chicago.

He was Attending Physician at Augustana Hospital, 1903 to 1925, Cook County Hospital, 1912 to 1913, and Assistant Professor of Medicine, University of Illinois Medical School, 1922 to 1929. He was a member of the Illinois Medical Society, Chicago Medical Society, Chicago Society of Internal Medicine, Institute of Medicine, American Medical Association and a Fellow of the American College of Physicians since 1920.

In 1925, Dr. Frick became Chief of Staff of Augustana Hospital and served in this capacity until his retirement in 1938. He died at the Augustana Hospital on May 9, 1946, at the age of 78.

Dr. Frick was an internist who represented the highest in the fine tradition of medical men of the older school. He was an upright gentleman, kind and understanding, and it was with great respect that patients and fellow physicians approached him. He was a capable teacher and trained many young men in the practice of general medicine.

With the passing of Dr. Frick, we have lost one who in every real way combined the finest qualities of both the old and new in the medical world.

ROBERT W. KEETON, M.D., F.A.C.P.

DR. ALEX MORTON ROSENBLUM

Dr. Alex Morton Rosenblum (Associate), Youngstown, Ohio, died September 6, 1946, of myocardial infarction.

Dr. Rosenblum was born on January 6, 1890. He graduated in Medicine from the University of Pennsylvania School of Medicine, Philadelphia, in 1912. For a number of years he was on the staff of the St. Elizabeth's Hospital. He served during World War I.

Dr. Rosenblum was a member of the Mahoning County Medical Society and the Ohio State Medical Association, and a Fellow of the American Medical Association. He became a member of the American Congress on Internal Medicine in 1920, and when that organization was merged with The American College of Physicians, Dr. Rosenblum automatically became an Associate of the latter.

DR. WAYNE WILLIAM BISSELL

Wayne William Bissell, Rockford, Illinois, was born in Lodi, Wisconsin, June 18, 1886. He took his pre-medical work at the University of Wisconsin from 1905 to 1909, and graduated from Rush Medical College in 1911. He served as intern at the Cook County Hospital, and later as a pathologist, 1913-1916. In July, 1916, he was appointed to the staff of the Mayo Clinic and remained there until World War I, when he accompanied the Mayo Unit in France. Since then he has served as pathologist and roentgenologist in Columbia, South Carolina; Reading, Pennsylvania, and New Castle, Pennsylvania. In September of 1945, he came to Rockford, where he served as pathologist at the Rockford Memorial Hospital.

Dr. Bissell was the author of a number of published papers; member of county and state medical societies and A.M.A.; Fellow of the American College of Physicians since 1931. He died of a coronary attack on September 6, 1946. He had the respect of his medical associates, and will be greatly missed.

CECIL M. JACK, M.D., F.A.C.P.,
Governor for Southern Illinois

DR. LEWIS TILGHMAN STONEBURNER, III

Dr. Lewis Tilghman Stoneburner, III, of Richmond, Va., is presumed to have died in action with the Army of the United States on November 10, 1944. This represents all the information available from the War Department.

Dr. Stoneburner was born in Richmond, Va., March 2, 1913. He received his B.A. degree from the University of Richmond and his degree of Doctor of Medicine from the Medical College of Virginia, 1937.

He was an Assistant in Medicine at Harvard Medical School, 1939-40, and from 1940 to the time of his entry into the Army he was an Assistant in Medicine at the Medical College of Virginia, Richmond. Dr. Stoneburner was Assistant Physician to the Hospitals of the Medical College of Virginia and a member of the medical staff of the Sheltering Arms Hospital.

He was a member of the Richmond Academy of Medicine, the Virginia Medical Society, and a Fellow of the American Medical Association. He had been an Associate of The American College of Physicians since 1943. He was the son of Dr. Lewis Tilghman Stoneburner, Jr., of Richmond, Va.

He was a Captain in the Medical Corps of the Army of the United States. He is reported to have taken off from Algiers to Tunis aboard a B-25 bomber as a passenger. He had been detached from General Hospital No. 45 and was attached to Medical Headquarters under Colonel Perrin Hamilton Long. His duties were to visit the various hospitals and secure certain data for the high medical command. Nothing was ever heard from the plane after its departure.

DR. JULIUS ORD ARNSON

Dr. Julius Ord Arnson, aged 58, died Tuesday, October 29, 1946, after an illness of one week. He was born in Eau Claire, Wisconsin, on July 3, 1888, of Norwegian parentage. He graduated from high school there, attended Hamline University, the University of Minnesota and was graduated from Northwestern University Medical School in 1911.

Dr. Arnson interned at St. Barnabas Hospital in Minneapolis after which he practiced in Kimball, Minnesota, before entering upon his specialty.

Well known throughout the Missouri Slope area, he came to Bismarck in 1915 where he was associated with the Quain and Ramstad Clinic in internal medicine and which department he headed. He was a leading heart specialist of the Northwest and saved the lives of an untold number of people with the same disease of which he himself succumbed.

He did postgraduate work in Boston, Massachusetts, and during World War I he was on the medical staff of Base Hospital 64, serving in France. He was a member of the American Legion, Sixth District Medical Society, North Dakota State Medical Association, American Medical Association, and a Fellow of the American College of Physicians of which he was Governor for many years. He was an associate editor of the Journal-Lancet, a member of the Blue Lodge and a 32nd degree Scottish Rite Mason.

For many years he was physician to the North Dakota State Penitentiary, which added to his labors as a busy internist. He only did this as a contribution to man. He made many visits to large penal institutions of this country in order to gain information as to the best method of treating these unfortunates, and applied the principles which he had learned with the limited facilities he had to work with.

Dr. Arnson was not only a competent physician but a humanitarian and a philanthropist. He despised sham and hypocrisy and was outspoken in his convictions. He was especially kind to the underprivileged.

Dr. Arnson never married, but maintained a home for his friends, as he was a most gracious and unselfish host. He had only one survivor, Dr. J. M. Arnson of Benson, Minnesota.

He had a marked natural literary ability, and he anticipated retiring on his ranch—which was his only hobby—where he had intended to write his memoirs of a prairie physician, for he had accumulated many letters and personal poems which he had planned to embody in this contribution.

Dr. Arnson was modest and never sought publicity for his good deeds, and had only a few confidants who knew of his personal affairs.

He had no particular religious affiliations, but his contributions to various church and civic organizations go unreported. His living deeds adorn his memory as he was a true brother of man.

C. W. SCHOREGGE, M.D., Bismarck, N. D.

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